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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR BENZYL ALCOHOL

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OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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16. ABSTRACT

Health and Environmental Effects Documents (HEEDS) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference Doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. In the case of suspected carcinogens, RfDs may not be estimated. Instead, a carcinogenic potency factor, or q_1^*, is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA.

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include: Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level which would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval which does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980a) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986a, respectively.

EXECUTIVE SUMMARY

Benzyl alcohol is a colorless liquid with a mild aromatic odor (Ringk and Theimer, 1981). It is soluble in most organic solvents such as chloroform, ether, glycerol and alcohol, and is moderately soluble in water (Sax and Lewis, 1987). Benzyl alcohol is usually produced commercially by the catalytic hydrolysis of benzyl chloride, although reduction of benzoic acid or benzoic acid derivatives is also feasible (Ringk and Theimer, 1979). Chemical Dynamics Corporation, ICI Americal Holdings Inc. (Agricultural Products Group) and Kalama Chemical Inc. currently manufacture benzyl alcohol (SRI, 1988; USITC 1987, 1988); a large proportion is used in flavorings and fragrances (SRI, 1988). Benzyl alcohol is also used in development of color photographic film, as a solvent for dyestuffs, inks and cosmetics and in the preservation of parenteral drugs and medical syrups, ointments and aerosols (Ringk and Theimer, 1979; Sax and Lewis, 1987).

In the atmosphere, benzyl alcohol probably exists almost entirely in the vapor phase (Eisenreich et al., 1981). Apparently, the gas-phase reaction with photochemically produced hydroxyl radicals is the primary atmospheric degradation pathway (half-life of ~2 days) (Atkinson, 1985). Wet deposition may also occur. The reactions both with ozone and with direct photochemical degradation are not expected to be important fate processes.

In water, the dominant fate process is probably microbial degradation. Benzyl alcohol rapidly degraded in water under aerobic (Belly and Goodhue, 1976; Dore et al., 1975; Shelton and Tiedje, 1984; Urano and Kato, 1986) and anaerobic (Balba et al., 1981; Horowitz et al., 1982) conditions in the laboratory. Photolysis, hydrolysis, volatilization to the atmosphere and

chemical oxidation are all expected to be slow processes in water. Adsorption to sediment and suspended organic matter, as well as bioaccumulation in fish and aquatic organisms, are probably not important fate processes.

Benzyl alcohol occurs naturally in some foods (Coleman et al., 1981; Dumont and Adda, 1978; Ho et al., 1983; Kinlin et al., 1972; Takeoka et al., 1988). It is also a man-made compound used predominantly in flavorings and fragrances, household remedies and other common household products (Ringk and Theimer, 1979; Sax and Lewis, 1987). Although quantitative information is lacking, available data suggest that the general population may be exposed to benzyl alcohol primarily by inhalation. Exposure can also occur by ingestion and dermal contact during the use of products in which it is contained.

Benzyl alcohol can be released to the environment by various pathways. Primary sources of release include wastewater emissions from its manufacture, formulation and use in commercial products (Dagon, 1973; Keith, 1976), effluent from sewage treatment plants (Ellis et al., 1982; Gossett et al., 1983) and landfill leaching (Albaiges et al., 1986; Harmsen, 1983). Benzyl alcohol was detected in incinerator emissions and exhaust of gasoline and diesel engines (Hampton et al., 1982; Mulawa and Cadle, 1981; Seizinger and Dimitriades, 1972; James et al., 1984).

Benzyl alcohol was considerably more toxic to bluegills (LC_{50} = 10 mg/ℓ) and tidewater silversides (LC_{50} = 15 mg/ℓ) in a study by Dawson et al. (1977) than it was to fathead minnows (LC_{50} = 460 mg/ℓ) in a study by Mattson et al. (1976). These differences may be species-related, but the fact that two low values were reported in one study and one high value was reported in another study suggests that differences in experimental procedures between studies could have affected the results. An

male mice at ≥500 mg/kg and in female mice at ≥1000 mg/kg (NTP, 1988). No histopathological effects attributable to treatment were noted in either sex of either species. Effects on rats and mice from 91-day treatment at doses of 0, 50, 100, 200, 400 and 800 mg/kg given 5 days/week were similar to the shorter-term experiment. There was increased mortality at the highest dosage in male rats and female mice (and possibly female rats); other deaths were attributed to the gavage procedure. Signs of neurotoxicity followed dosing at the 800 mg/kg level in rats and mice, but this was considered an acute effect. Mean body weights of the highest dosage rats of both sexes and the female mice receiving ≥400 mg/kg were slightly lower than controls. Male rats at the 800 mg/kg level exhibited histopathological effects of the hippocampus, thymus, kidney, skeletal muscle, as well as unusual bleeding; females rats at this dose also showed necrosis of the hippocampus. No histopathological effects attributable to treatment were seen in the mice.

Chronic oral studies consisted of the NTP-sponsored 103-week gavage studies using rats and mice (NTP, 1988), and a developmental toxicity and reproduction study using mice by Hazelden (1983). In the NTP (1988) study, rats and mice of both sexes were given doses of 0, 200 and 400 mg/kg and 0, 100 and 200 mg/kg, respectively, administered 5 days/week for 2 years. Survival of the female rats at both dose levels was significantly lower than that of vehicle controls. However, many of the deaths were judged to be gavage-related, and not compound-related. The higher incidence of accidental death in the dosed animals is likely a result of the combined effect of the gavage procedure simultaneous with the neurotoxic effect of the compound. High-dose male rats had a higher incidence of epithelial hyperplasia of the forestomach, and a squamous cell papilloma was seen in one male rat in the high- and low-dose groups. In female mice, survival in

the high-dose group was significantly higher than in controls after the 74th week. Survival was not different between other groups of either sex. Although mice were treated with lower doses of benzyl alcohol, they still appear to be the less sensitive species, since there were no toxicologically significant effects even at the 200 mg/kg dose, which did produce systemic effects in the rats.

In acute studies, rats died within 14 days after exposure to 1000 ppm (4422 mg/m³) of benzyl alcohol for 8 hours (Smyth et al., 1951). Single oral dose LD_{50}s in animals range from ~1000-2000 mg/kg (Jenner et al., 1964; Graham and Kuizenga, 1945). The average survival time of cats was 22 hours from one 20 mℓ application of 100% benzyl alcohol to their shaved backs (Graham and Kuizenga, 1945). Cats have a pronounced sensitivity to drugs containing benzene rings that is due, in part, to a relative deficiency in their ability to detoxify xenobiotics by glucuronic acid conjugation (Wilcke, 1984). An acute dermal LD_{50} of <5.0 mℓ/kg was reported for guinea pigs (Jones, 1967). Benzyl alcohol has been reported to cause severe eye problems following its use in ocular surgery (Grant, 1974), some dermal irritation to rabbits and humans (Motoyoshi et al., 1979), hypersensitivity reactions (Grant et al., 1982; Shmunes, 1984; Wilson et al., 1986) and contact allergies in humans (Fisher, 1975; Edwards, 1981; Lazzarini, 1982; Shoji, 1983; Van Joost et al., 1985).

A higher incidence of preterm infant mortality resulted from intravascular and intramuscular administration of drugs containing benzyl alcohol as a preservative, so that dosages averaged 191 mg/kg/day (Brown et al., 1982).

No information was found regarding carcinogenicity from inhalation exposure to benzyl alcohol. A 2-year gavage study using rats and mice with doses of 0, 200 and 400 mg/kg, and 0, 100 and 200 mg/kg, respectively, was negative for carcinogenicity under the conditions of the study (NTP, 1988).

Benzyl alcohol was negative in reverse mutation assays with S. typhimurium, with and without metabolic activating systems, (Mortelmans et al., 1986; Florin et al., 1980; Rogan et al., 1986; Ishidate et al., 1984), and in tests with E. coli WP2 uvrA, but it caused DNA damage in a rec assay with B. subtillis (Kuroda et al., 1984; Yoo, 1986). It was negative in an micronucleus test in ddY mice (Hayashi et al., 1988), in mammalian cell culture (Ishidate et al., 1988), and did not induce DNA damage in human alveolar cells (Waters et al., 1982). In the mouse L5178Y/tk$^{+/-}$ lymphoma forward mutation assay, results were equivocal (McGregor et al., 1988).

In a reproductive and developmental toxicity study, gavaged doses of 750 mg/kg/day given to pregnant mice for gestation days 7-14 resulted in lower mean litter and pup weights, and signs of maternal toxicity including lower mean body weights and increased mortality (Hazelden, 1983; Hardin et al., 1987).

As data regarding the subchronic and chronic toxicity and carcinogenicity of inhalation exposure to benzyl alcohol were not available, it was not possible to derive RfDs or q_1*s for this route of exposure. There was equivocal evidence of carcinogenicity in mice exposed to benzyl alcohol by gavage for 2 years. Therefore, benzyl alcohol was classified in Group D - not classifiable as to human carcinogenicity. A subchronic oral RfD of 1.0 mg/kg/day was derived based on the NOAEL of 200 mg/kg, 5 days/week for 13 weeks in the NTP (1988) subchronic rat study. A chronic oral RfD of 0.3 mg/kg/day was derived based on the LOAEL of 200 mg/kg 5 days/week for 2 years in the NTP (1988) study. An RQ of 1000 was derived, also based on the LOAEL of 200 mg/kg 5 days/week in the NTP (1988) chronic study.

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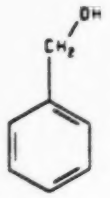
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
GI	Gastrointestinal
GMAV	Genus mean acute value
GMCV	Genus mean chronic value
HPLC	High-performance liquid chromatography
K	Partition coefficient
K_{oc}	Soil/sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted concentration levels)
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MNPCE	Micronucleated polychromatic erythrocytes
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
PCE	Polychromatic erythrocytes
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
SPF	Specific pathogen free
THOD	Theoretical oxygen demand
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Benzyl alcohol is also known as α-hydroxy toluene, benzene methanol, phenylcarbinol and hydroxymethyl benzene (Chemline, 1989; CAS, 1989; SANSS, 1989). The structure, CAS number, molecular weight and empirical formula for benzyl alcohol are as follows:



CAS Registry number: 100-51-6

Empirical formula: C_7H_8O

Molecular weight: 108.13

1.2. CHEMICAL AND PHYSICAL PROPERTIES

Benzyl alcohol is a colorless liquid with a mild aromatic odor (Ringk and Theimer, 1979). In its purest state, it has the distinct odor of a rose. It is soluble in most organic solvents such as chloroform, ether, glycerol and alcohol (Ringk and Theimer, 1979; Sax and Lewis, 1987). Selected physical properties of benzyl alcohol are as follows:

Melting point:	-15.3°C	Weast et al., 1988
Boiling point:	205.3°C	Weast et al., 1988
Density:	1.0419 g/mℓ	Weast et al., 1988
Vapor Pressure at 25°C:	0.11 mm Hg	Riddick et al., 1986
Water Solubility at 25°C:	40.00 g/ℓ	Ringk and Theimer, 1979
Log K_{OW}:	1.10	Hansch and Leo, 1985

Flash point:	105°C	Sax and Lewis, 1987
Conversion factor at 25°C:	1 ppm = 4.40 mg/m³	

Benzyl alcohol is readily esterified with a variety of organic acids in the presence of an acid catalyst. It can be readily oxidized to the corresponding aldehyde, and under vigorous conditions, it can be oxidized to benzoic acid. Benzyl alcohol can also be catalytically hydrogenated, producing toluene (Ringk and Theimer, 1979).

1.3. PRODUCTION DATA

Benzyl alcohol is commercially prepared by the alkaline hydrolysis of benzyl chloride using sodium carbonate (Ringk and Theimer, 1979). Benzyl alcohol can also be prepared by the hydrolysis of benzyl chloride using other catalysts, by the Grignard or related metalation reactions with benzyl chloride and by the reduction of benzoic acid, benzoic acid derivatives or benzaldehyde. During 1977, 24 U.S. manufacturing plants produced 115-1150 thousand pounds of benzyl alcohol (ISCAPP, 1989). The primary manufacturing site was Monroe Chemical, Inc., Eddystone, DE. Current U.S. manufacturers of benzyl alcohol are Chemical Dynamics Corp., South Plainfield, NJ; ICI Agricultural Products Group, Edison, NJ; and Kalama Chemicals, Inc., Seattle, WA (SRI, 1988; USITC, 1987, 1988). More current U.S. production data were not located in the available literature cited in Appendix A.

1.4. USE DATA

Benzyl alcohol is used in photographic developers for color films, as a degreasing agent in rug cleaners and as a solvent for dyestuffs, ballpoint pen inks, cellulose esters, casein, waxes, etc. It is also used to preserve aqueous and oily parenteral drugs in cough syrups, ointments, insect ointments and repellents, dermatological aerosol sprays, and ophthalmic,

burn and dental solutions. Cosmetics such as nail lacquers and hair dyes contain benzyl alcohol, as well. The aliphatic esters of benzyl alcohol are used in flavorings, fragrances, soaps and perfumes (Ringk and Theimer, 1979; Sax and Lewis, 1987).

1.5. SUMMARY

Benzyl alcohol is a colorless liquid with a mild aromatic odor (Ringk and Theimer, 1979). It is soluble in most organic solvents such as chloroform, ether, glycerol and alcohol, and is moderately soluble in water (Sax and Lewis, 1987). Benzyl alcohol is usually produced commercially by the catalytic hydrolysis of benzyl chloride, although reduction of benzoic acid or benzoic acid derivatives is also feasible (Ringk and Theimer, 1979). Three companies currently manufacture benzyl alcohol (SRI, 1988; USITC 1987, 1988); a large proportion is used in flavorings and fragrances (SRI, 1988). Benzyl alcohol is also used in development of color photographic film, as a solvent for dyestuffs, inks and cosmetics and in the preservation of parenteral drugs and medical syrups, ointments and aerosols (Ringk and Theimer, 1979; Sax and Lewis, 1987).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Based on a vapor pressure of 0.11 mm Hg at 25°C (Riddick et al., 1986), benzyl alcohol is expected to exist almost entirely in the vapor phase in the ambient atmosphere (Eisenreich et al., 1981).

2.1.1. **Reaction with Hydroxyl Radicals.** Using the method of Atkinson (1985), the half-life for the gas-phase reaction of benzyl alcohol with photochemically produced hydroxyl radicals in the atmosphere can be estimated at 2 days, based on a calculated rate constant of 5.11×10^{-11} cm^3/molecule-sec and an average atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm^3. This process is probably the most important atmospheric fate process for benzyl alcohol.

2.1.2. **Reaction with Ozone.** Benzyl alcohol is not susceptible to oxidation by ozone in the atmosphere (Atkinson, 1985; U.S. EPA, 1987).

2.1.3. **Physical Removal Processes.** Based on its water solubility, 40 g/ℓ (Ringk and Theimer, 1979), benzyl alcohol may undergo dissolution into clouds and subsequently be removed from the atmosphere in precipitation.

2.1.4. **Photolysis.** The direct photochemical degradation of benzyl alcohol in the atmosphere is not expected to be an important fate process.

2.2. WATER

2.2.1. **Hydrolysis.** Benzyl alcohol probably does not undergo hydrolysis since it contains no hydrolyzable functional groups (Lyman et al., 1982).

2.2.2. **Oxidation.** Based on the experimentally determined rate constant for the reaction of benzyl alcohol with alkylperoxy radicals, 2.4 ℓ/mol-s (Hendry et al., 1974), and an estimated alkylperoxy concentration in water of 1×10^{-9} mol/ℓ (Mill et al., 1980), the half-life for this reaction is

9 years. The half-life for the reaction of benzyl alcohol with photochemically produced hydroxyl radicals in water can be estimated at ~100 days using an experimentally determined rate constant of 8.4×10^9 ℓ/mol-s (Dorfman and Adams, 1973) and a optimal hydroxyl radical concentration of 1×10^{-17} mol/ℓ in natural waters (Mill et al., 1980).

2.2.3. **Photolysis.** No reaction was observed during a 4-hour sunlight irradiation of benzyl alcohol in water (Draper and Crosby, 1983). Thus, direct photochemical degradation of benzyl alcohol in water is probably not an important fate process.

2.2.4. **Microbial Degradation.** Benzyl alcohol underwent 60.8% degradation in a 5-day test using a sewage sludge inoculum under aerobic conditions (Belly and Goodhue, 1976). In a screening test, benzyl alcohol underwent >75% aerobic degradation within 8 weeks using a sewage sludge inoculum (Shelton and Tiedje, 1984). Benzyl alcohol (100 mg/ℓ) underwent 79% and 87% degradation after 5.4 and 8.3 days, respectively, under aerobic conditions using a sewage seed (Urano and Kato, 1986). In a 5-day test, benzyl alcohol underwent 33% biological THOD using a sewage inoculum (Dore et al., 1975). These studies suggest rapid aerobic biodegradation in environmental waters.

Benzyl alcohol underwent fast biodegradation after a 2-month acclimation period under anaerobic conditions using a salt marsh sediment inoculum (Balba et al., 1981). Anaerobic biodegradation for benzyl alcohol using a sludge seed from two different waste treatment plants was complete within 2 weeks (Horowitz et al., 1982). However, the sampling frequency was not reported; thus, it is not clear at what rate benzyl alcohol underwent degradation.

2.2.5. **Bioconcentration.** The BCF for benzyl alcohol is 4.04, based on the log K_{ow}, 1.81 (Hansch and Leo, 1985). The regression equation, log BCF = 0.76 log K_{ow} - 0.23, was used in this determination (Lyman et al., 1982). This value suggests that concentration in fish and aquatic organisms is not an important fate process.

2.2.6. **Adsorption.** Based on experimental K_{oc} values in soil that ranged from <5-16 (Briggs, 1981; Southworth and Keller, 1986), adsorption to sediment and suspended organic material is not expected to be an important fate process.

2.2.7. **Volatilization.** Based on benzyl alcohol's water solubility, 40 g/ℓ at 25°C (Ringk and Theimer, 1979), and its vapor pressure of 4.1×10^{-9} mm Hg 40 g/ℓ at 25°C (Riddick et al., 1986), a Henry's Law constant of 3.91×10^{-7} atm m³/molecule at 25°C can be calculated (Lyman et al., 1982). Using the bond method of Hine and Mookerjee (1975), a Henry's Law constant of 2.28×10^{-7} atm • m³/molecule at 25°C can be obtained. These values suggest that volatilization of benzyl alcohol from water is not an important fate process. The estimated volatilization half-life from a model river 1 m deep, flowing 1 m/sec, with a wind velocity of 3 m/sec is 97 days, based on the smaller of the above Henry's Law constants (Lyman et al., 1982).

2.3. SOIL

2.3.1. **Microbial Degradation.** Pertinent data regarding the degradation of benzyl alcohol in soil were not located in the available literature cited in Appendix A. Bacteria obtained from soil and grown on phenol or toluene degraded benzyl alcohol (Chambers et al., 1963; Claus and Walker, 1964; Kramer and Doetsch, 1950). In water, biodegradation of benzyl alcohol would probably occur rapidly under both aerobic and anaerobic conditions, suggesting rapid biodegradation in soil.

2.3.2. **Adsorption/Leaching.** Experimental K_{oc} values for benzyl alcohol range from <5-26.9 (Briggs, 1981; Southworth and Keller, 1986), suggesting high mobility in soil for benzyl alcohol (Swann et al., 1983)

2.3.3. **Volatilization.** The relatively high vapor pressure for benzyl alcohol, 0.11 mm Hg at 25°C (Riddick et al., 1986), suggests that volatilization from dry soil is an important fate process. However, volatilization from moist or wet soil may not be significant.

2.4. SUMMARY

In the atmosphere, benzyl alcohol probably exists almost entirely in the vapor phase (Eisenreich et al., 1981). Apparently, the gas-phase reaction with photochemically produced hydroxyl radicals is the primary atmospheric degradation pathway (half-life of ~2 days) (Atkinson, 1985). Wet deposition may also occur. The reactions both with ozone and with direct photochemical degradation are not expected to be important fate processes.

In water, the dominant fate process is probably microbial degradation. Benzyl alcohol rapidly degraded in water under aerobic (Belly and Goodhue, 1976; Dore et al., 1975; Shelton and Tiedje, 1984; Urano and Kato, 1986) and anaerobic (Balba et al., 1981; Horowitz et al., 1982) conditions in the laboratory. Photolysis, hydrolysis, volatilization to the atmosphere and chemical oxidation are all expected to be slow processes in water. Adsorption to sediment and suspended organic matter, as well as bioaccumulation in fish and aquatic organisms, are probably not important fate processes.

In soil, benzyl alcohol displays high mobility and readily leaches through soil (Briggs, 1981; Southworth and Keller, 1986; Swann et al., 1983). Microbial degradation in soil may occur; however, conclusive data were not located in the available literature. Volatilization from dry soil to the atmosphere may be an important fate process; however, it is probably not an important process in wet soils.

3. EXPOSURE

Benzyl alcohol results from both natural and anthropogenic activity. It is found in various foods and is used in a wide range of applications. Primary sources of release include losses in wastewater and fugitive emissions during its commercial manufacture and formulation.

The National Occupational Exposure Survey estimated that 203,108 workers are exposed to benzyl alcohol (NIOSH, 1984). Based on the available monitoring and use data, the general population apparently would be exposed to benzyl alcohol by inhalation, dermal contact and ingestion during the use of common household products in which it is contained. Minor exposure can occur through the ingestion of food in which benzyl alcohol occurs naturally.

3.1. WATER

Quantitative monitoring data for benzyl alcohol in water are limited. Benzyl alcohol was identified in wastewater effluent from the photographic processing industry (Dagon, 1973) and Kraft paper mills in 6/8 samples at $\leq$0.013 mg/ℓ (Keith, 1976). Benzyl alcohol was qualitatively identified in secondary effluent from wastewater treatment plants (Ellis et al., 1982). The effluent from a Los Angeles County wastewater treatment plant contained 500 µg/ℓ of benzyl alcohol (Gossett et al., 1983).

Benzyl alcohol was detected in leachate from a Barcelona, Spain, sanitary landfill (Albaiges et al., 1986) and from a municipal refuse disposal site in the Netherlands (Harmsen, 1983).

3.2. FOOD

Benzyl alcohol is a volatile flavor component of baked potatoes (Coleman et al., 1981), Beaufort (Gruyere) cheese (Dumont and Adda, 1978), bacon (Ho et al., 1983) and roasted filberts (Kinlin et al., 1972). It is also a

volatile component of blended nectarines, but was not identified in a headspace analysis of the intact fruit (Takeoka et al., 1988). These monitoring data indicate that the general population can be exposed to small amounts of benzyl alcohol by ingesting these foods; however, quantitative information is not available.

3.3. INHALATION

Pertinent data regarding the ambient concentration of benzyl alcohol in the atmosphere were not located in the available literature cited in Appendix A. Benzyl alcohol was found in the gaseous effluent from four waste incinerators (James et al., 1984) and in gasoline and diesel engine exhaust (Hampton et al., 1982; Mulawa and Cadle, 1981; Seizinger and Dimitriades, 1972).

3.4. DERMAL

Pertinent data regarding dermal exposure to benzyl alcohol were not located in the available literature cited in Appendix A. Benzyl alcohol is used in perfumes, ointments, ophthalmic and burn solutions, insect ointments and repellents, dermatological aerosol sprays, cosmetics and the preservation of aqueous and oily parenteral drugs (Ringk and Theimer, 1979; Sax and Lewis, 1987). Use of these products results in dermal exposure.

3.5. OTHER

Benzyl alcohol is also used in flavorings, cough syrups and dental solutions (Ringk and Theimer, 1979; Sax and Lewis, 1987). Exposure to benzyl alcohol may occur during the use of these products.

3.6. SUMMARY

Benzyl alcohol occurs naturally in some foods (Coleman et al., 1981; Dumont and Adda, 1978; Ho et al., 1983; Kinlin et al., 1972; Takeoka et al., 1988). It is also a man-made compound used predominantly in flavorings and

fragrances, household remedies and other common household products (Ringk and Theimer, 1979; Sax and Lewis, 1987). Although quantitative information is lacking, available data suggest that the general population may be exposed to benzyl alcohol primarily by inhalation. Exposure can also occur by ingestion and dermal contact during the use of products in which it is contained.

Benzyl alcohol can be released to the environment by various pathways. Primary sources of release include wastewater emissions from its manufacture, formulation and use in commercial products (Dagon, 1973; Keith, 1976), effluent from sewage treatment plants (Ellis et al., 1982; Gossett et al., 1983) and landfill leaching (Albaiges et al., 1986; Harmsen, 1983). Benzyl alcohol was detected in incinerator emissions and exhaust of gasoline and diesel engines (Hampton et al., 1982; Mulawa and Cadle, 1981; Seizinger and Dimitriades, 1972; James et al., 1984).

4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. Two tests of benzyl alcohol toxicity have been performed in freshwater invertebrates. Knie et al. (1983) reported an EC_{50} for immobilization of water fleas, Daphnia magna, by benzyl alcohol of 400 mg/ℓ. An EC_0 of 300 mg/ℓ and an EC_{100} of 500 mg/ℓ were also reported. No experimental details were provided. Sinniah (1983) studied the acute toxicity of benzyl alcohol to mosquito eggs and larvae. Eggs of Aedes aegypti and Aedes scutellaris, 5-14 days old and immersed in hay infusion, were exposed to various concentrations of benzyl alcohol for 24-72 hours. Water temperature was kept between 25 and 27°C. Results were similar in eggs of both species, with LD_{50} values of 160 ℓ/hectare. Tests were also done using larvae and pupae. LD_{50} values of 105-110 ℓ/hectare were reported in first instar larvae. Third and fourth instar larvae were less sensitive, with LD_{50} values of 126-129 ℓ/hectare. Concentrations ≤500 ℓ/hectare failed to produce mortality in pupae.

LC_{50} values have been calculated for several species of freshwater fish. The acute toxicity of benzyl alcohol to fathead minnows, Pimephales promelas, was determined by Mattson et al. (1976). Juvenile fathead minnows, ranging in age from 4-8 weeks and in length from 1.1-3.1 cm, were exposed to benzyl alcohol in a static nonrenewal test. The temperature of the water varied between 18 and 22°C. Twenty fish (two groups of 10) were tested at each of 3-5 nominal concentrations. The 1-, 24-, 48-, 72- and 96-hour LC_{50} values were 770, 770, 770, 480 and 460 mg/ℓ, respectively. Toxicity was much higher in bluegill sunfish, Lepomis macrochirus, in a static acute test conducted by Dawson et al. (1977). Bluegill, which varied from 33-75 mm in length, were exposed to nominal concentrations of 5-56 ppm

(mg/ℓ) of benzyl alcohol for 96 hours at 23°C. The 96-hour LC_{50} was 10 ppm (mg/ℓ). Knie et al. (1983) reported an LC_{50} of 646 mg/ℓ in golden orfe, Leuciscus idus. The LC_0 was 630 mg/ℓ and the LC_{100} was 662 mg/ℓ. No experimental details of this study were provided.

Several toxicity screening studies have been conducted in freshwater fish. Larval sea lampreys, Petromyzon marinus, varying in length from 7.5-12.5 cm, were exposed to 5 mg/ℓ of benzyl alcohol for 24 hours under static conditions at 13°C (Applegate et al., 1957). No effects were seen in the two lampreys tested. Exposure to 5 mg/ℓ of benzyl alcohol did not have toxic effects on bluegill sunfish, Lepomis macrochirus, goldfish, Carassius auratas, or trout, Salmo trutta, in similar studies (Hollis and Lennon, 1954; Wood, 1954). In one study, benzyl alcohol was forcefed to carp, Cyprinus carpio, at doses of 127-136 mg/kg bw using gelatin capsules (Loeb and Kelly, 1963). The fish, which weighed an average of 1.4 kg, were placed in 18°C running spring water for observation. No effects were noted after 48 hours in the three fish tested.

One study of the acute toxicity of benzyl alcohol to a marine species was located in the literature. Tidewater silversides, Menidia beryllina, ranging in length from 40-100 mm, were exposed to nominal concentrations of 10-32 ppm (mg/ℓ) benzyl alcohol under static conditions at 20°C (Dawson et al., 1977). The 96-hour LC_{50} was estimated to be 15 ppm (mg/ℓ).

4.1.2. Chronic Effects on Fauna.

4.1.2.1. **TOXICITY** -- Pertinent data regarding the effects of chronic exposure of aquatic fauna to benzyl alcohol were not located in the available literature cited in Appendix A.

4.1.2.2. **BIOACCUMULATION/BIOCONCENTRATION** -- Pertinent data regarding the bioaccumulation/bioconcentration potential of benzyl alcohol in aquatic fauna were not located in the available literature cited in Appendix A.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- The effects of benzyl alcohol on photosynthesis, nitrogenase activity and growth in algae were studied by Stratton and Corke (1982). Blue-green algae, Anabaena inaequalis, Anabaena cylindrica and Anabaena variabilis, and green algae, Chlorella pyrenoidosa and Scenedesmus quadricauda, were tested. The 3-hour EC_{50} for photosynthetic effects, measured by uptake of $^{14}CO_2$ from $NaH^{14}CO_3$, was >100 ppm (mg/ℓ) in all five species. The 5-hour EC_{50} for inhibition of nitrogenase activity, measured by acetylene reduction, in A. inaequalis and A. cylindrica also exceeded 100 ppm (mg/ℓ). Growth, calculated from absorbance values, was unaffected by 12- to 14-day exposures to benzyl alcohol concentrations of 10 ppm (mg/ℓ) in any of these species. A second study of the effects of benzyl alcohol on algae was conducted on Haematococcus pluvialis by Knie et al. (1983). The EC_{50} for reduced growth was 2600 mg/ℓ in this study. No experimental details were provided.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration potential of benzyl alcohol in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria. A few studies have investigated the toxicity of benzyl alcohol to bacteria. The acute toxicity of benzyl alcohol to Photobacterium phosphoreum was measured by Kaiser et al. (1987) using the Microtox test. The 30-minute EC_{50} for light reduction in the bacterial suspensions was 0.66 mM (71.4 mg/ℓ). Effects were produced at higher concentrations in other studies. A cell multiplication test was conducted in Pseudomonas putida by Knie et al. (1983). The EC_{10} for effects of benzyl alcohol was 658 mg/ℓ. Vaishnav, (1986) investigated the effect of benzyl alcohol on the biodegredation rate of a mixed microbial culture. The EC_{50} for rate reduction was 0.047 mol/ℓ (5083 mg/ℓ).

Family	TEST TYPE		
	GMAV[a] (mg/L)	GMCV[a] (mg/L)	BCF[a]
#1 Chordate (Salmonid-fish)	NA	NA	NA
#2 Chordate (warmwater fish)	10[b]	NA	NA
#3 Chordate (fish or amphibian)	460[c]	NA	NA
#4 Crustacean (planktonic)	NA	NA	NA
#5 Crustacean (benthic)	NA	NA	NA
#6 Insectan	NA	NA	NA
#7 non-Arthropod/-Chordate	NA	NA	NA
#8 New Insectan or phylum representative	NA	NA	NA
#9 Algae	NA	>100[d]	NA
#10 Vascular plant	NA	NA	NA

[a]NA=Not available
[b]LC_{50} for bluegill sunfish, Lepomis macrochirus
[c]LC_{50} for fathead minnow, Pimephales promelas
[d]EC_{50} for effects on photosynthesis and nitrogenase activity in the blue-green alga, Anabaena inaequalis

FIGURE 4-1

Organization Chart for Listing GMAVs, GMCVs and BCFs Required to Derive Numerical Water Quality Criteria by the Method of U.S. EPA/OWRS (1986) for the Protection of Freshwater Aquatic Life from Exposure to Benzyl Alcohol

The lack of pertinent data regarding the effects of exposure of aquatic fauna and flora to benzyl alcohol precluded the development of a saltwater criterion (U.S. EPA/OWRS, 1986). Available data are shown in Figure 4-2. Additional data required for the development of a saltwater criterion include the results of acute assays with a chordate species, a nonarthropod and nonchordate species, a mysid or panaeid crustacean, three additional nonchordate species and one other species of marine fauna. The development of a saltwater criterion also requires data from three chronic toxicity tests, one test on a species of algae or vascular plant and one bioconcentration study.

4.5. SUMMARY

Benzyl alcohol was considerably more toxic to bluegills (LC_{50} = 10 mg/ℓ) and tidewater silversides (LC_{50} = 15 mg/ℓ) in a study by Dawson et al. (1977) than it was to fathead minnows (LC_{50} = 460 mg/ℓ) in a study by Mattson et al. (1976). These differences may be species-related, but the facts that two low values were reported in one study and one high value was reported in another study suggest that differences in experimental procedures could have affected the results. An LC_{50} of 646 mg/ℓ was reported in golden orfe (Knie et al., 1983), but lack of details prevented assessment of this study. No effects were reported in larval sea lamprey (Applegate et al., 1957), bluegill, goldfish or trout (Hollis and Lennon, 1954; Wood, 1954) acutely exposed to 5 mg/ℓ of benzyl alcohol in screening-type studies. Among invertebrates, an EC_{50} of 400 mg/ℓ was reported for Daphnia immobilization (Knie et al., 1983), and LD_{50} values of 105-160 ℓ/hectare were reported in mosquitos (Sinniah, 1983). Among algae, the EC_{50} values for effects on photosynthesis and nitrogenase activity exceeded 100 mg/ℓ in all five species tested (Stration and Corke,

Family	TEST TYPE		
	GMAV[a] (mg/L)	GMCV[a] (mg/L)	BCF[a]
#1 Chordate	15[b]	NA	NA
#2 Chordate	NA	NA	NA
#3 non-Arthropod/-Chordate	NA	NA	NA
#4 Crustacean (Mysid/Penaeid)	NA	NA	NA
#5 non-Chordate	NA	NA	NA
#6 non-Chordate	NA	NA	NA
#7 non-Chordate	NA	NA	NA
#8 Other	NA	NA	NA
#9 Algae	NA	NA	NA
#10 Vascular plant	NA	NA	NA

[a]NA = Not available
[b]LC_{50} for tidewater silverside, Menidia beryllina

FIGURE 4-2

Organization Chart for Listing GMAVs, GMCVs and BCFs Required to Derive Numerical Water Quality Criteria by the Method of U.S. EPA (1986a) Protect Saltwater Aquatic Life from Exposure to Benzyl Alcohol

1982). The EC_{50} for reduced growth was 2600 mg/ℓ in one species (Knie et al., 1983). Effects in bacteria were reported at concentrations ranging from 71.4-5083 mg/ℓ (Kaiser et al., 1987; Knie et al., 1983; Vaishnav, 1986). Studies of terrestrial organisms showed that 131 mg/ℓ of benzyl alcohol inhibited spore germination in fungi (Wilson et al., 1987) and that LD_{50} values were $\geq$100 mg/kg bw in two species of birds (Schafer et al., 1983).

5. PHARMACOKINETICS

5.1. ABSORPTION

Pertinent data regarding the extent and rate of absorption of benzyl alcohol from inhalation exposure were not located in the available literature cited in Appendix A.

Benzyl alcohol administered orally by stomach tube to rabbits in a 450 mg/kg dose was rapidly absorbed, as measured by urinary excretion of hippuric acid at 65.7 and 72.8% of the dose at 6 and 24 hours, respectively (Diack and Lewis, 1928). A 1000 mg dose of an aqueous suspension given to a rabbit by stomach tube was similarly absorbed by the excretion of 82% of the dose as either glucuronides or ether-soluble acids (Bray et al., 1951). In another gavage study in rabbits, compounds found in the urine after 24 hours accounted for 98% of a 250 mg/kg dose of benzyl alcohol, indicating rapid absorption of the compound (Bray et al., 1958). Humans also were found to absorb a major portion of a 1500-2000 mg dose given orally, as shown by the excretion of 74-88% of the dose as hippuric acid (Snapper et al., 1924).

In an <u>in vitro</u> study of the percutaneous penetration of ^{14}C-labeled benzyl alcohol in human autopsy skin (Menczel and Maibach, 1970), absorption was measured in an absorption cell as the percent of dose applied to the epidermal layer of the skin that was found in the normal saline dermal perfusate after 5 days. Benzyl-7-^{14}C-alcohol (2.7 mg) was dissolved in 50 µℓ benzene. The amount of benzyl alcohol that diffused through the skin ranged from 4.45-32.74%, with the variation thought to be related to the thickness of the dermal layer. A large proportion of the benzyl alcohol remained in the epidermal layer of skin, even after the 5-day experimental period. The ratio of dermal to epidermal retention was generally <1 (mean of 0.76 for five experiments). In a study using the same methods (Menczel

and Maibach, 1972), the dermal/saline solution equilibrium concentration of benzyl-7-^{14}C-alcohol ranged from 0.232-0.270, and conformed well with the K of 0.254. The stratum corneum retained the major portion of benzyl alcohol that was partitioned into the epidermis.

5.2. DISTRIBUTION

Pertinent data regarding the distribution of benzyl alcohol following inhalation or oral exposure were not located in the available literature cited in Appendix A.

Kimura et al. (1971) administered benzyl alcohol in intravenous doses of 52 and 105 mg/kg to unanesthetized beagles of both sexes. The plasma half-life was ~1.5 hours. The calculated apparent volume of distribution, 11 ℓ/kg, suggested that the major portion of the drug was distributed in the tissues.

5.3. METABOLISM

A number of older studies reported that benzyl alcohol was rapidly oxidized to benzoic acid, which was then conjugated with glycine and excreted by the kidney as hippuric acid in animals and man (Snapper et al., 1924; Diack and Lewis, 1928; Stekol, 1939). Conjugation of benzoic with glycine is catalyzed by glycine acyltransferase in the mitochondrial fraction of the liver (Lebel et al., 1988).

Several studies of benzyl alcohol metabolism from oral administration have been performed with rabbits. Diack and Lewis (1928) administered benzyl alcohol to male rabbits by stomach tube (448-450 mg, expressed as equivalent dose of benzoic acid/kg bw) and found that it was rapidly oxidized to benzoic acid and excreted in the urine as hippuric acid, accounting for 65.7% and 72.8% of the dose at 6 and 24 hours, respectively.

Administration of 450 mg/kg sodium benzoate to the rabbits resulted in similar recoveries, which indicated that the oxidation of benzyl alcohol to benzoic acid occurred at least as rapidly as the formation and elimination of hippuric acid. A rabbit given 1000 mg of an aqueous benzyl alcohol suspension by stomach tube excreted 82% of the dose as either glucuronides (24% of excreted amount) or ether-soluble acids (76% of excreted amount); however, when doses of 500-1600 mg were administered with glycine, the glucuronide fraction dropped to 2-9%, and the ether-soluble fraction increased to 91-98% of the excreted dose (Bray et al., 1951). When the initial rate of benzyl alcohol conversion was greater than the maximum rate of glycine conjugation, benzoic acid was found in the blood. Bray et al. (1958) investigated the metabolism of benzyl alcohol (suspended in water) administered by stomach tube to rabbits in doses of 250 mg/kg. The compounds found in urine after 24 hours, as a percent of the dose (means of 4-6 experiments), were 2% mercapturic acid, 74% glycine conjugates, 8% copper-reducing material (as glucuronic acid) and 14% glucosiduronic acid, accounting for 98% of the dose. Humans on a pure milk and flour diet given 1500-2000 mg orally of benzyl alcohol excreted 74-88% of the dose as hippuric acid (Snapper et al., 1924).

McCloskey et al. (1986) gave intraperitoneal injections of 500-1100 mg/kg of benzyl alcohol (10% in peanut oil, v/v) to adult CD-1 male mice. Benzyl alcohol appeared in the plasma within minutes of administration at levels of 11.0-208.4 g/mℓ. Significant levels of benzaldehyde, an intermediate in the oxidation, were also found in plasma of mice 5 minutes after doses of benzyl alcohol >700 mg/kg were administered. Benzaldehyde plasma concentrations of 4.2-15.0 g/mℓ resulted from doses of 700-1100 mg/kg, with no benzaldehyde detected in the plasma following doses <700 mg/kg.

Neither benzyl alcohol nor benzaldehyde was found in the plasma of control mice injected with either saline or peanut oil. At 4 hours after intraperitoneal injection of adults and neonates with benzyl alcohol at 1000 mg/kg, plasma levels were 60-70 µg/mℓ for benzyl alcohol and 15-16 µg/mℓ for benzaldehyde in both age groups. No differences were detected in the pattern of metabolism between mature and neonatal mice. Pretreatment of the mice with pyrazole, an inhibitor of alcohol dehydrogenase and the enzyme responsible for the conversion of benzyl alcohol to benzaldehyde, increased levels of benzyl alcohol in the plasma. Pretreatment of the mice with disulfiram, which inhibits aldehyde dehydrogenase, the enzyme involved in the conversion of benzaldehyde to benzoic acid, markedly increased plasma benzaldehyde levels to 3 times that of controls.

In metabolism studies of subcutaneously administered benzyl alcohol, two rabbits injected with 1000 mg of benzyl alcohol excreted 300-400 mg of hippuric acid in the urine after 24 hours (Stekol, 1939). Stekol (1939) injected three rats subcutaneously with 500 mg/kg bw benzyl alcohol and found that the substance isolated from pooled 48-hour urine samples was hippuric acid (percent of dose not specified).

In a study of benzyl alcohol metabolism and elimination, 14 term (8 male, 6 female) and 9 preterm (5 male, 4 female) neonates received intravenous or intramuscular loading doses of phenobarbital containing benzyl alcohol (Lebel et al., 1988). Benzoic acid accumulated in the serum more in preterm infants than in term infants, as determined by 10-fold higher normalized peak level when measured by HPLC ($p<0.001$). Also, preterm infants were found to have greater percentages of benzoic acid and less hippuric acid in the urine after doses of benzyl alcohol than term infants.

It has been suggested that the immature livers or kidneys of preterm infants may have a reduced capacity to detoxify by glycine conjugation the amount of benzoic acid produced from the oxidation of benzyl alcohol.

Gershanik et al. (1982) administered benzyl alcohol (0.9%) to neonates at a level of 99-234 mg/kg. The compound was found in the serum at a mean concentration of 1.01±0.13 mmol/ℓ. Mean benzoic acid and hippuric acid concentrations in the urine were 0.377±0.119 and 1.469±0.25 mmol/ℓ, respectively. In infants that had not received benzyl alcohol, benzoic acid and hippuric acid were found in the urine at much lower levels (0.029±0.009 and 0.765-0.089 mmol/ℓ, respectively).

An *in vitro* metabolism study using guinea pig liver microsomes (Sloane, 1965) showed that ^{14}C-phenol could be formed from ^{14}C-benzyl alcohol (ring-labeled); there was no microsomal metabolism of benzoic acid (in the presence of NADPH) to phenol.

5.4. EXCRETION

Orally administered benzyl alcohol is converted to benzoic acid, which is then conjugated with glycine and excreted in the urine as hippuric acid in animals and man (Snapper et al., 1924; Diack and Lewis, 1928). In the study by Diack and Lewis (1928), 450 mg of benzyl alcohol administered to male rabbits by stomach tube was accounted for as hippuric acid in the urine at 65.7 and 72.8% of the dose at 6 and 24 hours, respectively. Doses of 250 mg/kg administered to rabbits by gavage were recovered in the urine after 24 hours as (percent of dose): 2% mercapturic acid, 74% glycine conjugates, 8% copper-reducing material (as glucuronic acid) and 14% glucosiduronic acid, accounting for 98% of the dose (Bray et al., 1958). A dose of 1000 mg given by stomach tube to one rabbit was excreted as either glucuronides (24% of excreted amount) or ether-soluble acids (76% of excreted amount), accounting

for 82% of the dose, while glycine administered with 500-1600 mg of benzyl alcohol resulted in the glucuronide fraction dropping to 2-9% and the ether-soluble fraction rising to 91-98% of the excreted material (Bray et al., 1951). Humans given 1500-2000 mg of benzyl alcohol orally while on a pure milk and flour diet excreted 74-88% of the dose as hippuric acid (Snapper et al., 1924).

Following intraperitoneal injections of benzyl alcohol in peanut oil to adult and neonatal mice, McCloskey et al. (1986) suggested that benzyl alcohol was eliminated by saturable kinetics, so that small increases in dosages would result in disproportionate levels in the plasma.

Subcutaneously administered benzyl alcohol, in dosages of 1000 mg given in three portions 2 hours apart to rabbits, was recovered in the urine as 300-400 mg of hippuric acid after 24 hours (Stekol, 1939).

5.5. SUMMARY

No data were found regarding the extent and rate of absorption of benzyl alcohol from inhalation exposures. Benzyl alcohol was rapidly absorbed from orally administered doses in rabbits (Diack and Lewis, 1928; Bray et al., 1951, 1958) and man (Snapper et al., 1924). An *in vitro* study of percutaneous penetration of ^{14}C-benzyl alcohol indicated that a major portion of the compound remained in the stratum corneum of the epidermal layer of human skin.

No information was found regarding distribution of benzyl alcohol following inhalation or oral exposure. In dogs, the calculated apparent volume of distribution suggested that the major portion of intravenously administered benzyl alcohol was distributed in the tissues (Kimura et al., 1971).

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure. Workers occupationally exposed for an undetermined duration to a high vapor concentration of a mixture containing benzyl alcohol, benzene and ester solvents reported temporary headaches, vertigo, nausea, diarrhea and weight loss (Treon and Stasik, 1983).

6.1.1.1. SUBCHRONIC -- Pertinent data regarding toxicity from subchronic inhalation exposure of benzyl alcohol were not located in the available literature cited in Appendix A.

6.1.1.2. CHRONIC -- Pertinent data regarding toxicity from chronic inhalation exposure of benzyl alcohol were not located in the available literature cited in Appendix A.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- In 16-day and 13-week studies, F344/N rats and B6C3F1 mice were gavaged with technical-grade benzyl alcohol (99% pure) suspended in corn oil (NTP, 1988). In the shorter experiment, groups of five males and five females of each species, 8 weeks old at the start of the study, were administered 0 (vehicle only), 125, 250, 500, 1000 and 2000 mg/kg 5 days/week for 12 doses. (Animals in the 125 mg/kg dose groups were unintentionally administered a 10-fold higher dose on days 8 and 9 of treatment.) Animals were observed twice daily and were weighed initially and once a week. All animals were necropsied at the conclusion of the study, and histologic examinations were performed on three male and two female rats and four male mice in the 500 mg/kg dose group and on three female mice in the 1000 mg/kg dose group. All rats in the 2000 mg/kg dose group and 2/5 males and 3/5 females in the 1000 mg/kg dose group died before completion of the study. At the end of the study, mean body weight of the

male rats in the 1000 mg/kg dose group was 18% lower than that of the controls. Rats receiving the two highest dosages were lethargic and had blood around the nose and mouth and in the urinary and gastrointestinal tracts; these rats also had hemorrhages under the skin. Males in the 500 and 1000 mg/kg dose groups, and females in the 250 and 500 mg/kg dose groups, had rough hair coats. There were no histopathologic effects attributable to treatment in any rats at any dosage level.

Effects in mice from the 16-day gavage study were similar to those found in rats. All mice at the 2000 mg/kg level, and 1/5 males and 2/5 females at the 1000 mg/kg dosage level, died before completion of the study. Male mice receiving 500, 1000 and 2000 mg/kg and female mice receiving 1000 and 2000 mg/kg benzyl alcohol were lethargic and had rough hair coats. At necropsy, blood was found in the urinary bladder of mice in the 1000 and 2000 mg/kg dose groups. Histopathologic effects attributable to treatment were not found in any mice at any dosage level.

In the 13-week studies, groups of 10 male and 10 female rats and mice were dosed with 0 (vehicle only), 50, 100, 200, 400 and 800 mg/kg of benzyl alcohol 5 days a week for the duration of the experiment. Rats were 7-8 weeks old and mice were 7-9 weeks old when placed on the study. Animals were observed twice daily, weighed individually at the beginning and end of the study and weighed as groups once a week during the study. Moribund animals were sacrificed. All animals were necropsied; those in the control groups and the 800 mg/kg treatment groups were examined histopathologically. Microscopic examinations of the brains were performed on animals in the 400 mg/kg treatment groups of both species and on all mice that died before termination of the study. Following dosing by gavage, 8/10 male rats administered 800 mg/kg and one given 200 mg/kg died; four of the deaths at the

highest dose were attributed to the gavage procedure. In the female rats, one vehicle control, one in the 400 mg/kg dose group and two in the 800 mg/kg dose group died after being dosed; all deaths except one at the highest dose were accidental. Following treatment, rats of both sexes in the 800 mg/kg dose group showed signs of neurotoxicity including staggering, labored breathing and lethargy; at the end of the study, they had mean body weights lower than that of vehicle controls (7% lower for males, 5% lower for females). Five of 10 males in this dose group had blood around the nose and mouth after 8 weeks of treatment. At this dose level, histopathologic effects attributable to treatment included necrosis of the dentate gyrus of the hippocampus in 9/9 males and 7/7 females. Skeletal muscle necrosis (5/10), thymic congestion, hemorrhage and atrophy (8/10) and nephrosis in the kidney (6/9) were also observed in male rats at this highest dosage level.

In mice, no deaths were observed in the control groups, in the two lower dosage groups in males or in the 200 mg/kg dose group in females; one or two deaths were seen in the other dosage groups, but the only deaths not related to the gavage procedure were of two females in the high-dose group. Final mean body weights were 5 and 8% less than those of vehicle controls in the 400 and 800 mg/kg female dose groups, respectively; all other groups had mean body weights within 5% of controls. In the first 2 weeks of the study, male and female mice staggered after receiving the 800 mg/kg dosage. No histopathologic effects attributable to treatment were seen in the mice. All groups had some mice with a chronic interstitial pneumonia, which is characteristic of a Sendai infection.

6.1.2.2. CHRONIC -- Two-year toxicology and carcinogenesis studies on benzyl alcohol were conducted using groups of 50 male and 50 female F344/N

rats and B6C3F1 mice (NTP, 1988). Technical-grade benzyl alcohol (99% pure) mixed in corn oil was administered by gavage 5 days/week for 103 weeks to rats in dosages of 0 (vehicle control), 200 and 400 mg/kg, and to mice in dosages of 0, 100 and 200 mg/kg. Although mice in the 100 and 200 mg/kg treatment groups were unintentionally dosed with 375 and 750 mg/kg α-methylbenzyl alcohol for 4 days during week 80, no adverse effects were noted. Animals were 8-9 weeks old when treatment began. Animals were observed twice a day; they were weighed initially, then once a week for 12 weeks and once a month thereafter. All animals were necropsied, and histologic examinations on a number of organs and tissues were performed on all female rats and on male rats and mice in the vehicle control and high-dose groups, male rats and mice that died before the 22nd month and male rats and mice with gross lesions. The pituitary gland and testes were examined in low-dose male rats; the adrenal gland, brain, kidney, liver and lung were examined in low-dose male mice; and the brain, liver, spleen and uterus were examined in low-dose female mice.

Survival of the benzyl alcohol-treated female rats at both dose levels was significantly lower than that of the vehicle controls, the low-dose group after week 71 and the high-dose group after week 50. However, many of the deaths in the treated rats, but considerably fewer in the controls, were related to the gavage procedure. Respectively, accidental and nonaccidental deaths in groups of 50 control, low- and high-dose female rats were 1, 13, 17, 16, 13 and 20. Survival of control and treated male rats and mean body weights for all rats within sex groups were generally comparable throughout the study. No clinical signs that could be attributed to the treatment were observed. Rats in control and treated groups at both dose levels exhibited swelling in the cervical region, pink eyes and red exudate around the eyes,

signs of sialodacryoadenitis, which was confirmed in sentinel animals. Rats in the high-dose groups showed an increased incidence of cataracts (males: control, 2/50; low dose, 3/50; high dose, 23/50; females: 2/50, 2/50, 16/50) and retinal atrophy (males: 1/50, 3/50, 24/50, females: 1/50, 3/50, 20/50), but this was attributed to those animals being housed in the cages on the top racks, permitting greater exposure to fluorescent lighting. High-dose male rats also had a higher incidence of epithelial hyperplasia of the forestomach (control, 0/48; low dose, 0/19; high dose, 4/50). Benzyl alcohol-treated rats that died before completion of the study had an increased incidence of hemorrhage and foreign material in the respiratory tract. Dose-related effects in the respiratory tracts of males included increases in acute inflammation in the nasal tract, hemorrhages in the larynx and edema in the lungs. Higher incidences of hemorrhage and foreign material in the lungs were seen in both male and female dosed rats.

In female mice, survival was significantly lower in the control group than in the high-dose group after the 74th week. Survival did not differ between other groups of either sex. High-dose male and female mice had an increased incidence of corpora amylacea (males: control, 15/49; low dose, 21/48; high dose, 22/50; females: 14/50, 15/48, 25/50), although this was noted to be "a common, spontaneously occurring lesion." High-dose male mice had an increased incidence of lung congestion, and low-dose male and female mice had an increased incidence of foreign material in the lungs; neither of these effects was statistically significant.

6.1.3. **Other Relevant Information.** In an acute inhalation study reported by Smyth et al. (1951), six rats (strain and sex not specified) were exposed to 1000 ppm benzyl alcohol for 8 hours and observed for 14 days. Three of the six rats died. The maximum time that rats could be exposed to saturated vapors of benzyl alcohol without death resulting was 2 hours.

Single oral dose LD_{50}s (intubated) of 2080 and 1040 mg of benzyl alcohol/kg bw were reported for rats (20 animals) and rabbits (9 animals), respectively (Graham and Kuizenga, 1945). Within 30 minutes of dosing, both rats and rabbits became prostrate until they died. Intubated benzyl alcohol resulted in acute oral LD_{50}s of 1230 mg/kg (95% confidence intervals of 1130-1330) in rats from a 100% solution and 1580 mg/kg (95% confidence intervals of 1410-1770) in mice from a 25% solution in corn oil (Jenner et al., 1964). In the rats, death occurred within 1 hour to 4 days; in mice, death resulted within 2-18 hours. Other signs of toxicity were depression in both rats and mice, coma within 10-15 minutes in rats and excitability for 3-4 days in rats.

Gruber (1923) reported that pure benzyl alcohol in volumes of 2.5-10.8 mℓ administered by stomach tube to dogs weighing 12.5-27 kg caused catharsis and emesis, usually within minutes of dosing. In other studies, 1.0-5.0 mℓ of pure benzyl alcohol administered intraperitoneally to dogs and rabbits and intramuscularly to rabbits caused a marked increase in urine flow (Gruber, 1924).

Benzyl alcohol elicited an antiarrhythmic effect in dogs within 30-60 seconds after an intravenous injection of 0.1-0.4 mℓ/kg of a 4% solution (Eichbaum and Yasaka, 1976). A similar response in rats occurred after an injection of 0.2-0.6 mℓ/kg of 1-2% benzyl alcohol. In cats, subcutaneous administration of 50-100 mℓ/kg of lactated Ringer's solution containing 1.5% benzyl alcohol as a preservative (doses of benzyl alcohol were 392 and 660 mg/kg) resulted in toxic signs including ataxia, hyperesthesia, fasciculations of head and ear muscles, slight but increasingly severe depression, coma, respiratory failure, convulsions and death (Cullison et al., 1983).

Lower doses produced a slower advancement of signs and longer progression, but death resulted in all cases. Cats apparently have a pronounced sensitivity to drugs containing benzene rings, particularly phenol. This is due, in part, to a relative deficiency in their ability to detoxify xenobiotics by glucuronic acid conjugation because of a lack of UDP-glucuronyltransferase activity with respect to some substrates (Wilcke, 1984).

Jones (1967) reported an acute dermal LD_{50} of <5.0 mℓ/kg in guinea pigs. Cats were particularly sensitive to dermal application of benzyl alcohol, with an average survival time of 22 hours (two animals) after one 20 mℓ application of 100% benzyl alcohol to their shaved backs (Graham and Kuizenga, 1945). Signs of toxicity included excessive salivation and twitching at the site of application. Later, animals exhibited generalized tremor, muscular incoordination, hind limb paralysis and violent convulsions, sometimes leading to prostration, and then respiratory failure and death. The cats' body weights decreased by 200-400 g, but probably from inability to eat and drink.

Grant (1974) reported that "severe striate keratopathy developed, progressing to chronic edema of the cornea, with vesicles, bullae and dirty pigmented appearance of the endothelium" following intraocular use of a benzyl alcohol-preserved saline solution during cataract surgery in humans.

In a comparative study of the irritancy of synthetic perfumes to the skin of animals and humans, Motoyoshi et al. (1979) found that benzyl alcohol (>97% pure) had little or no irritation response in guinea pigs or miniature swine, but was moderately irritating to rabbits when applied at 100% concentration; in humans, benzyl alcohol was mildly irritating when applied to the skin in a 32% solution in acetone. In these tests, no correlation was found between the animal and human tests for the synthetic perfumes.

Hypersensitivity reactions in humans have been reported after the parenteral administration of injectable drugs or diluents containing benzyl alcohol as a bacteriostatic agent. Grant et al. (1982) noted that a 55-year-old man showed symptoms including sudden onset of fatigue, nausea and diffuse angioedema following an intramuscular injection of vitamin B_{12} that contained benzyl alcohol as a preservative. A skin test consisting of intracutaneous injections of vitamin B_{12}, with and without benzyl alcohol (0.9%) as a preservative, and saline with benzyl alcohol revealed a positive wheal-and-flare response only to the solutions containing benzyl alcohol. Signs of an allergic dermatitis (erythema, palpable edema and raised borders) were seen in a 46-year-old woman treated with sodium tetradecyl sulfate, formulated with 1% benzyl alcohol (Shmunes, 1984). A patch test of 5% benzyl alcohol in petrolatum showed a moderately severe response at 48 hours, while a patch test of the injectable treatment solution containing 1% benzyl alcohol was negative. In another case, a 49-year-old male patient developed a hypersensitivity reaction characterized by fever and a maculo-papular rash on the chest and arms after receiving three different injections for antineoplastic chemotherapy, all preserved with benzyl alcohol (Wilson et al., 1986). The sensitivity was also confirmed with skin testing.

Contact allergies have also been reported following use of benzyl alcohol-containing topical solutions or creams. A 36-year-old woman and a 43-year-old man developed contact dermatitis at the site of application of a perfume and an aftershave lotion, respectively, both of which contained benzyl alcohol (Fisher, 1975). Both patients responded positively to patch tests with 1% benzyl alcohol in petrolatum, but negatively to scratch, intradermal and subcutaneous injections of 1% benzyl alcohol in saline.

Allergic reactions were also reported in a 44-year-old white woman using a sunscreen (Edwards, 1981), a 46-year-old woman being treated with a topical corticosteroid (Lazzarini, 1982) and a 41-year-old Japanese woman prescribed a cream for tinea pedis (Shoji, 1983). In all cases, the solutions contained benzyl alcohol, and all patients had a positive reaction to a patch test with benzyl alcohol in petrolatum. In a study of allergic reactions to a number of perfume ingredients, 4 of 242 patients reacted positively to a benzyl alcohol skin test (Van Joost et al., 1985).

Several reports describe toxicity in preterm neonates exposed intravascularly to solutions that contained benzyl alcohol as a preservative. Brown et al. (1982) gave details of 10 of 16 low birth weight infants (<1250 g) who died following exposure to bacteriostatic normal saline containing benzyl alcohol so that the amount of benzyl alcohol received was minimally 130 mg/kg/day, the average was 191 mg/kg/day and the maximum was 405 mg/kg/day. The symptoms of toxicity, seen between day 2 and 4 of administration, were slowly progressive bradycardia, often with gasping respiration (resulting in the name "gasping syndrome"), seizures, unresponsiveness and extremely depressed EEGs, characteristic of progressive metabolic acidosis. Gershanik et al. (1982) reported that 10 low birth weight or premature infants developed "gasping syndrome" following hospitalization and exposure to benzyl alcohol through administration of bacteriostatic saline.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding carcinogenicity from inhalation exposure to benzyl alcohol were not located in the available literature cited in Appendix A.

6.2.2. Oral. In 2-year toxicology and carcinogenesis studies using F344/N rats and B6C3F1 mice (see Section 6.1.2.2.), animals were gavaged 5

days/week with technical-grade benzyl alcohol (99% pure) suspended in corn oil to achieve concentrations of 0, 200 and 400 mg/kg for rats and 0, 100 and 200 mg/kg for mice (NTP, 1988). There was an increased incidence of epithelial hyperplasia in the forestomachs of the high dose male rats (control, 0/48; low dose, 0/19; high dose, 4/50), and 1/19 low-dose and 1/50 high-dose male rats had squamous cell papillomas in the same tissue. A negative trend was seen in the incidence of adenomas and adenomas or carcinomas (combined) of the anterior pituitary gland of female rats; vehicle controls had a higher incidence than the high-dose group.

There was a slightly increased incidence of adenomas of the adrenal cortex in high-dose male mice (control, 0/48; low dose, 0/44; high dose, 3/48; p=0.044 in life table and incidental tumor tests); despite the occurrence of this tumor being somewhat uncommon historically in corn oil-gavaged controls, the number that occurred was within the historical range, and therefore not attributed to the compound treatment. There was a negative trend of adenomas of the Harderian gland in male mice, but the incidences in the dosed groups were not significantly different from the vehicle controls.

6.2.3. Other Relevant Information. Pertinent data regarding the carcinogenicity from other routes of exposure to benzyl alcohol were not located in the available literature cited in Appendix A.

6.3. MUTAGENICITY

Benzyl alcohol has been tested for mutagenicity and clastogenicity in a number of assay systems. In a short-term mutagenicity test used by the NTP, benzyl alcohol (99.8% pure) was assayed at a minimum of five dose levels in a preincubation modification of the Salmonella/mammalian microsome assay (Mortelmans et al., 1986). It did not produce reverse mutations in

Salmonella typhimurium strains TA1535, TA1537, TA97, TA98 and TA100 in the presence or absence of Aroclor 1254-induced rat and hamster metabolic activating systems. Similar results were reported for benzyl alcohol (3 αmol/plate) by Florin et al. (1980) after testing constituents of tobacco smoke for mutagenicity in four strains of S. typhimurium with and without S-9 from Aroclor-induced rats. Rogan et al. (1986) also reported that benzyl alcohol was not mutagenic in two strains of S. typhimurium (TA98 and TA100), but the presence or absence of an activation system was not noted. Ishidate et al. (1984) also found benzyl alcohol to be negative at a maximum dose of 10 mg/plate in reverse mutation assays using S. typhimurium strains TA92, TA1535, TA100, TA1537, TA94 and TA98, with and without S-9 activation.

Benzyl alcohol was not mutagenic in E. coli WP2 uvrA. It exhibited antimutagenic activity in a test in E. coli WP2 uvrA (trp^-) pretreated with furylfuramide (AF-2) without a cytotoxic effect in the bacteria (1035 μg/mℓ reduced the number of AF-2-induced trp^- revertants to 50%), but did not suppress the mutagenic activity of N-methyl-N'-nitro-N-nitrosoguanidine. However, in a rec assay using Bacillus subtilis M45 (rec^-) and H17 (rec^+), benzyl alcohol was found to cause DNA damage to the organisms (Kuroda et al., 1984; Yoo, 1986). In an experiment designed to determine the practicality of using P3478 (pol A^-) E. coli, a repair-deficient mutant, in predicting the carcinogenic potential of compounds, benzyl alcohol gave a negative response at 10-50 μℓ and had reduced toxicity when tested with metabolic activation at 10 μℓ (Fluck et al., 1976).

In a micronucleus test conducted in six 8-week-old male ddY mice, benzyl alcohol was administered in a single intraperitoneal injection (Hayashi et al., 1988). From each mouse, 1000 PCEs were scored at low and high power, and the number of MNPCEs was noted. The ratio of PCEs to total erythrocytes

was also determined. Concurrent negative and positive controls, as well as historical control data from the testing laboratory, were evaluated to determine a true spontaneous level of frequencies of MNPCEs. Benzyl alcohol was negative in the in vitro chromosomal aberration test, meaning that the total incidence of cells with aberrations (including gaps) was ≤4.9%. Ishidate et al. (1988) also reported negative results when benzyl alcohol was tested in mammalian cell culture at 1000 µg/mℓ (9.2 mM) for 48 hours.

Waters et al. (1982) found that benzyl alcohol did not induce DNA damage, nor did it inhibit growth of human alveolar cells, A549, when added to the medium at ≤0.5 mM concentration.

The evidence for mutagenicity of benzyl alcohol was equivocal in the L5178Y tk^{+}/tk^{-} mouse lymphoma cell forward mutation assay (McGregor et al., 1988).

6.4. DEVELOPMENTAL TOXICITY

The only information available on teratogenicity of benzyl alcohol is from a study in chick embryos injected with 0.01-0.02 mℓ of undiluted benzyl alcohol either before incubation or within the first 7 days of incubation (Duraiswami, 1953). There were a number of embryonic abnormalities, but because many of the treated embryos did not survive to day 11 of incubation, and an anatomic and physiologic maternal-fetal relationship is lacking, this test was judged unsuitable for determining teratogenic risk to humans.

6.5. OTHER REPRODUCTIVE EFFECTS

Benzyl alcohol was tested in mice for possible embryotoxic, fetotoxic and neonatal toxic responses in a study that screened compounds for potential reproductive hazard (Hazelden, 1983; Hardin et al., 1987). Fifty SPF, pregnant female CD-1 mice, 42-60 days old at the start of the study,

were gavaged with benzyl alcohol mixed in distilled water at 750 mg/kg bw, the MTD in this strain of mice. Fifty mice given only vehicle were used as controls. Mice were treated from gestation days 7-14, the period of maximum organogenesis. Mice were observed once daily for clinical signs and twice daily for mortality. Mice that died were not necropsied. Body weights of the dams were recorded initially, on gestation days 7 (which determined the daily dosage) and 18, and on day 3 postpartum. Pups/litter and total litter weights were recorded within 12 hours of parturition (day 1 postpartum) and again 48 hours later. Three indices of reproductive performance determined for the compound and the concurrent vehicle control included: reporductive index = number of animals pregnant/number mated; gestation index = number of pregnancies resulting in live pups/number of pregnancies; viability index = number of pups alive on day 3 post partum/number alive on day 1 postpartum. Reproductive and gestation indices and mean gestation lengths were not significantly different in treated and control mice. Mean day 18 maternal body weight was significantly less in treated mice than in controls for both unadjusted data ($p<0.05$) and data adjusted for day 1 postpartum litter size ($p<0.001$). Day 3 post partum maternal weight was less ($p<0.05$), and maternal body weight gain over the treatment period (gestation days 7-18) was less using both unadjusted ($p<0.05$) and adjusted data ($p<0.001$) when comparing treated animals with the vehicle controls. Differences from controls recorded in litter weight data included lower mean litter mean pup weight on day 1 postpartum ($p<0.01$); lower mean litter mean pup weight on day 3 postpartum ($p<0.001$); lower mean litter weight change days 1-3 postpartum ($p<0.05$); and lower mean litter mean pup weight change days 1-3 postpartum ($p<0.001$). Signs of maternal toxicity included increased dam mortality, cyanosis, dyspnea, hypothermia, behavioral pathologies and piloerection.

In a preliminary, short-term, *in vivo* developmental toxicity test in mice, benzyl alcohol was given a score of intermediate priority classification or "no decision" when rated according to maternal toxicity relative to five indices of potential developmental toxicity, i.e., the proportion of pregnant survivors that produced a litter of at least one live born pup, average litter size and pup weight at birth, and average pup survival and weight gain to 3 days of age (York et al., 1988). No other information was given.

6.6. SUMMARY

No information was located regarding subchronic or chronic exposure to benzyl alcohol by inhalation. Systemic effects from a 16-day gavage study using male and female F344/N rats and B6C3F1 mice at doses of 0, 125, 250, 500, 1000 and 2000 mg/kg given 5 days/week included increased mortality and lethargy in both species at doses ≥1000 mg/kg, mean body weights 18% lower than controls in male rats receiving 1000 mg/kg, unusual bleeding in male rats and mice at ≥1000 mg/kg and rough hair coats in male rats at the 500 and 1000 mg/kg, in female rats at 250 and 500 mg/kg, in male mice at ≥500 mg/kg and in female mice at ≥1000 mg/kg (NTP, 1988). No histopathological effects attributable to treatment were noted in either sex of either species. Effects on rats and mice from 91-day treatment at doses of 0, 50, 100, 200, 400 and 800 mg/kg given 5 days/week were similar to the shorter-term experiment. There was increased mortality at the highest dosage in male rats and female mice (and possibly female rats); other deaths were attributed to the gavage procedure. Signs of neurotoxicity followed dosing at 800 mg/kg in rats and mice, but this was considered an acute effect. Mean body weights of the highest dosage rats of both sexes and the female mice receiving ≥400 mg/kg were slightly lower than those of controls. Male

rats at the 800 mg/kg level exhibited histopathological effects of the hippocampus, thymus, kidney and skeletal muscle, as well as unusual bleeding; female rats at this dose also showed necrosis of the hippocampus. No histopathological effects attributable to treatment were seen in the mice.

Chronic oral studies consisted of 103-week gavage studies in rats and mice (NTP, 1988) and a developmental toxicity and reproduction study in mice by Hazelden (1983). In the NTP (1988) study, rats and mice of both sexes were given doses of 0, 200 and 400 mg/kg and 0, 100 and 200 mg/kg, respectively, administered 5 days/week for 2 years. Survival of the female rats at both dose levels was significantly lower than that of vehicle controls. However, many of the deaths were gavage-related and not compound-related. High-dose male rats had a higher incidence of epithelial hyperplasia of the forestomach, and a squamous cell papilloma was seen in one male rat in the high- and low-dose groups. In female mice, survival in the high-dose group was significantly higher than in controls after the 74th week. Survival did not differ among other groups of either sex. Although mice were treated with lower doses of benzyl alcohol, they were still the less sensitive species, since there were no toxicologically significant effects even at the 200 mg/kg dose, which produced systemic effects in the rats.

In acute studies, rats died within 14 days after exposure to 1000 ppm (4422 mg/m^3) of benzyl alcohol for 8 hours (Smyth et al., 1951). Single oral-dose LD_{50}s in animals range from ~1000-2000 mg/kg (Jenner et al., 1964; Graham and Kuizenga, 1945). The average survival time of cats was 22 hours from one 20 mℓ application of 100% benzyl alcohol to their shaved backs (Graham and Kuizenga, 1945). Cats have a pronounced sensitivity to drugs containing benzene rings is due, in part, to a relative deficiency in their ability to detoxify xenobiotics by glucuronic acid conjugation (Wilcke, 1984). An acute dermal LD_{50} of <5.0 mℓ/kg was reported for

guinea pigs (Jones, 1967). Benzyl alcohol reportedly causes severe eye problems following its use in ocular surgery (Grant, 1974), dermal irritation in rabbits and humans (Motoyoshi, 1979), hypersensitivity reactions (Grant et al., 1982; Shmunes, 1984; Wilson et al., 1986) and contact allergies in humans (Fisher, 1975; Edwards, 1981; Lazzarini, 1982; Shoji, 1983; Van Joost et al., 1985).

A higher incidence of preterm infant mortality resulted from intravascular and intramuscular administration of drugs containing benzyl alcohol as a preservative, so that dosages averaged 191 mg/kg/day (Brown et al., 1982).

No information was found regarding carcinogenicity from inhalation exposure to benzyl alcohol. A 2-year gavage study using rats and mice with doses of 0, 200 and 400 mg/kg, and 0, 100 and 200 mg/kg, respectively, was negative for carcinogenicity under the conditions of the study (NTP, 1988).

Benzyl alcohol was negative in reverse mutation assays with S. typhimurium, with and without metabolic activating systems (Mortelmans et al., 1986; Florin et al., 1980; Rogan et al., 1986; Ishidate et al., 1984) and in tests with E. coli WP2 uvrA, but it caused DNA damage in a rec assay with B. subtillis (Kuroda et al., 1984; Yoo, 1986). It was negative in a micronucleus test in ddY mice (Hayashi et al., 1988) and in mammalian cell culture (Ishidate et al., 1988). Benzyl alcohol did not induce DNA damage in human alveolar cells (Waters et al., 1982). In the mouse L5178Y/tk$^{+/-}$ lymphoma forward mutation assay, results were equivocal (McGregor et al., 1988).

In a reproductive and developmental toxicity study, gavaged doses of 750 mg/kg/day given to pregnant mice on gestation days 7-14 resulted in lower mean litter and pup weights, and signs of maternal toxicity including lower mean body weights and increased mortality (Hazelden, 1983; Hardin et al., 1987).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Flavor and Extract Manufacturers Association reported that benzyl alcohol was granted GRAS (generally recognized as safe) status (FEMA, 1965), and the FDA has approved its use in food (Opdyke, 1974).

Because of reports of fatalities in newborns weighing <2.5 g that had been exposed to benzyl alcohol through bacteriostatic solutions used for flushing intravenous catheters, the FDA recommended in a letter to pediatricians, hospital pharmacists and hospital administrators, that "solutions used to flush intravascular catheters or for diluting or reconstituting medications in newborns not contain benzyl alcohol or any other preservative" (Anonymous, 1982).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to benzyl alcohol were not located in the available literature cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of benzyl alcohol to animals or humans from inhalation exposure were not located in the available literature cited in Appendix A.

8.1.2. Oral. Benzyl alcohol was negative for carcinogenicity in 103-week gavage studies in rats at dosage levels of 200 and 400 mg/kg administered 5 days/week (143 and 286 mg/kg/day) and in mice at dosage levels of 100 and 200 mg/kg (71 and 143 mg/kg/day) (NTP, 1988).

8.1.3. Other Routes. Pertinent data regarding the carcinogenicity of benzyl alcohol to animals or humans from other routes of exposure were not located in the available literature cited in Appendix A.

8.1.4. Weight of Evidence. No data were located regarding the carcinogenicity of benzyl alcohol to humans. In a well designed and well conducted study, there was no evidence of carcinogenic activity from benzyl alcohol administered orally by gavage 5 days/week for 103 weeks to male or female F344/N rats at doses of 200 and 400 mg/kg, or to male or female B6C3F1 mice at doses of 100 and 200 mg/kg (NTP, 1988). Applying guidelines for carcinogenic risk assessment adopted by the U.S. EPA (1986b), benzyl alcohol is assigned to Group E, evidence of noncarcinogenicity for humans.

8.1.5. Quantitative Risk Estimates.

8.1.5.1. INHALATION -- A complete lack of data precludes estimation of carcinogenic potency of benzyl alcohol from inhalation exposure.

8.1.5.2. ORAL -- The only carcinogenicity data located regarding benzyl alcohol were the negative gavage studies in rats and mice by NTP (1988). Quantitative estimation of carcinogenic potency cannot be performed for oral exposure to benzyl alcohol.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME (SUBCHRONIC) -- Pertinent data regarding the subchronic inhalation toxicity of benzyl alcohol were not located in the available literature cited in Appendix A; therefore, derivation of an RfD for subchronic inhalation exposure is not possible.

8.2.1.2. CHRONIC -- Pertinent data regarding the chronic inhalation toxicity of benzyl alcohol were not located in the available literature cited in Appendix A; therefore, derivation of an RfD for chronic inhalation exposure is not possible.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME (SUBCHRONIC) -- Subchronic gavage studies on mice and rats were conducted for 16 days at dosages of 0, 125, 250, 500, 1000 and 2000 mg/kg given 5 days/week (converted doses: 0, 89, 179, 357, 714 and 1429 mg/kg/day) and 91 days at dosages of 0, 50, 100, 200, 400 and 800 mg/kg given 5 days/week (converted doses: 0, 36, 71, 1435, 286 and 571 mg/kg/day) (NTP, 1988). From the 16-day study, increased mortality was reported in rats and mice at doses of $\geq$1000 mg/kg (Recs. #13, 16). Other signs of toxicity at $\geq$1000 mg/kg in male rats included decreased body weights, lethargy, hemorrhaging under the skin and blood in the urinary and GI tracts (Rec. #13). At dosages of $\geq$500 mg/kg (LOAEL) in male rats (Rec. #14) and $\geq$250 mg/kg (LOAEL) in female rats (Rec. #17), rough hair coats were observed. No effects were seen in males at doses $\leq$250 or in females at doses $\leq$125 mg/kg (NOAELs) (Recs. #15, 18). Systemic effects in mice included increased mortality at dosages $\geq$1000 mg/kg (Rec. #19), and lethargy and rough hair coats in males at dose levels $\geq$500 mg/kg (LOAEL) (Rec. #20) and in females at dose levels $\geq$1000 mg/kg (Rec. #22). The highest dosages

were associated with blood in the urinary bladder in both sexes. No effects were seen in male mice at doses ≤250 mg/kg or in female mice at doses ≤500 mg/kg (NOAELs) (Recs. #21, 23).

In the 91-day study, adverse effects in the brain (hippocampus), thymus, kidney and skeletal muscle in male rats were reported at 800 mg/kg (Rec. #3) but not at lower doses. Female rats exhibited the same effect on the hippocampus at the same dose level (Rec. #4). Eight of 10 male rats in the 800 mg/kg dose group died, with four deaths judged to be accidental; there were two deaths in the female rats at this dosage level, with one death attributed to the gavage procedure. Rats of both sexes exhibited signs of neurotoxicity following dosing with ≥800 mg/kg. At this dose level, some decrease in final mean body weights was seen in both sexes, as well as histopathological effects in males, including necrosis in the hippocampus, skeletal muscle necrosis, thymic atrophy and kidney nephrosis. At the 400 mg/kg dose level (LOAEL), female rats had final mean body weights 9% lower than those of controls (Rec. #5). Effects in mice included increased mortality in females at the highest dosage and some decrease in final mean body weights of females given ≥400 mg/kg (Rec. #9). At the highest dosage, mice of both sexes exhibited signs of neurotoxicity following dosing.

In the 91-day study, a NOAEL of 143 mg/kg/day (200 mg/kg administered 5 days/week) (Rec. #2) was identified for female rats, which were the more sensitive sex. Applying an uncertainty factor of 100 (10 for interspecies extrapolation multiplied by 10 to protect unusually sensitive individuals) results in an RfD for subchronic oral exposure of 1.43 mg/kg/day, which is rounded to 1 mg/kg/day.

Confidence in the key study is high, with effects occurring in a dose-related manner. Therefore, confidence in the subchronic RfD is high.

8.2.2.2. **CHRONIC** -- Chronic gavage studies were conducted for 103 weeks on rats and mice at dosage levels of 0, 200 and 400 mg/kg and 0, 100 and 200 mg/kg, respectively, administered 5 days/week (NTP, 1988). Converted dosages calculated by multiplying by 5 (number of doses/week) and dividing by 7 (days/week) are: for rats, 0, 143 and 286 mg/kg/day and for mice, 0, 71 and 143 mg/kg/day. A dosage of 400 mg/kg (LOAEL) was associated with an increased incidence of hyperplasia of the epithelium of the forestomach in male rats (Rec. #11), with no effects observed in males at the lower dose of 200 mg/kg (Rec. #12). Both the 200 (Rec. #1) and 400 mg/kg doses were associated with increased mortality in female rats, but the ultimate cause of death remains in doubt. Deaths of many female rats in both dosage groups (low dose, 17; high dose, 13), but of only one in the control group, were attributed to accidental causes, i.e., the gavage procedure. NTP (1988), however, concluded that administration of benzyl alcohol reduced the survival of dosed female rats. There is no firm evidence that the mortality was or was not associated with the chemical or with a combined effect of the chemical and the method of administration. Therefore, the LOAEL of 286 mg/kg/day for male rats was identified as the appropriate dose from which an RfD can be derived (Rec. #11). Applying an uncertainty factor of 10 to extrapolate from rats to humans, 10 to protect unusually sensitive individuals and 10 to extrapolate from a LOAEL to a NOAEL results in a chronic oral RfD of 0.286 mg/kg/day, which is rounded to 0.3 mg/kg/day.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of benzyl alcohol was discussed in Chapter 6 and dose-response data are summarized in Table 9-1. The data available for deriving CSs are from chronic and subchronic gavage studies (NTP, 1988) and a reproductive toxicity study by Hazelden (1983). In the chronic oral studies, groups of 50 male and 50 female F344/N rats and B6C3F1 mice were gavaged with benzyl alcohol at dosages of 0, 200 and 400 mg/kg, and 0, 100 and 200 mg/kg, respectively, 5 days/week for 103 weeks. In the 91-day studies, groups of 10 F344/N rats and B6C3F1 mice of each sex were gavaged with benzyl alcohol at dosages of 0, 50, 100, 200, 400 and 800 mg/kg 5 days/week. Survival decreased in female rats at chronic exposures of $\geq$200 mg/kg for 2 years and in male rats exposed to 800 mg/kg for 91 days. Although increased mortality was observed in the male and female rats at the higher dose it was not specifically attributed to the chemical and may have been due to the gavage administration procedure. High-dose male rats had a higher incidence of epithelial hyperplasia of the forestomach compared with the controls. Other effects observed in male rats given 800 mg/kg for 91 days were necrosis of the dentate gyrus of the hippocampus, skeletal muscle necrosis, thymic congestion, hemorrhage, and atrophy and nephrosis of the kidney. Necrosis of the dentate gyrus of the hippocampus was also observed in female rats at this dosage level. A dosage of 400 mg/kg in rats and 800 mg/kg in mice, given 5 days/week for 91 days, was associated with decreased mean body weights. No signs of toxicity were observed in the mice at the dosage levels eliciting toxic effects in the rat, indicating that rats may be the more sensitive species.

TABLE 9-1

Oral (Gavage) Toxicity for Benzyl Alcohol

Species/ Strain	Sex/No.	Average Weight[a] (kg)	Vehicle/ Physical State	Purity	Exposure (mg/kg)	Transformed Animal Dose[b] (mg/kg/day)	Transformed Human Dose[a] (mg/kg/day)	Response	Reference
Rat/ F344/N	M/50	0.41	corn oil	99%	400 5 days/week for 103 weeks	286	51.55	Hyperplasia of the epithelium of the forestomach	NTP, 1988
Rat/ F344/N	F/10	0.14	corn oil	99%	400 5 days/week for 13 weeks	286	36.03	Mean body weights 9% lower than those of controls	NTP, 1988
Rat/ F344/N	M/10	0.22	corn oil	99%	800 5 days/week for 13 weeks	571	83.64	Skeletal muscle necrosis, necrosis of hippocampus, atrophy of thymus	NTP, 1988
Mouse/ B6C3F1	F/10	0.022	corn oil	99%	800 5 days/week for 13 weeks	571	38.82	Mean body weights 8% lower than those of controls	NTP, 1988
Mouse/ SPF CD-1	F/50	0.033	distilled water	NR	750 for days 7-14 of gestation	750	58.40	Decreased mean litter and pup weights	Hazelden, 1983

[a]Time-weighted averages calculated from reported body weights

[b]Calculated by expanding the dose over a 7-day week

[c]Calculation: transformed animal dosage (mg/kg/day) x [animal body weight (kg)/reference human body weight (70 kg)]$^{1/3}$

NR = Not reported

In the study by Hazelden (1983), a dosage of 750 mg/kg/day administered by gavage to pregnant CD-1 mice for gestation days 7-14 was associated with decreased mean litter and pup weights, maternal toxicity and mortality. Although mortality was observed in these mice, the deaths were a result of acute exposure to a high dose in this strain.

Table 9-1 summarizes the toxicity data of benzyl alcohol. Table 9-2 presents the CSs and RQs derived associated with each effect presented in Table 9-1. The guidelines for calculation of a chronic toxicity RQ (U.S. EPA, 1984) recommend the use of chronic data, if adequate. Hence the RQ of 1000 associated with increased hyperplasia of the epithelium of the forestomach in male rats is most appropriately chosen to represent the chronic toxicity of benzyl alcohol (Table 9-3).

9.2. BASED ON CARCINOGENICITY

As reviewed in Chapter 6, carcinogenicity data for benzyl alcohol are limited to gavage studies in rats and mice conducted for the NTP (1988). In this study there was an increase in tumors of the adrenal cortex in male mice (3/48 high dose vs. 0/48 control; p=0.044 in life table and incidental tumor tests). Although 3/48 was considered by NTP to be within the range of historical controls, these results should be considered equivocal evidence of carcinogenic activity rather than negative. It is suggested, therefore, based on U.S. EPA (1986) guidelines that benzyl alchol could be assigned to Group D. Since potency factors cannot be derived for this chemical, a hazard ranking based on carcinogencity is not possible for this compound.

TABLE 9-2

Composite Scores for Orally Administered Benzyl Alcohol

Species/ Strain	Transformed Animal Dose (mg/kg/day)	Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rat/ F344/N	286	3605.2	1	Hyperplasia of the epithelium of the forestomach	6	6	1000	NTP, 1988
Rat/ F344/N	286	2520.0	1	Mean body weight lower than those of controls	3	3	5000	NTP, 1988
Rat/ F344/N	571	5859.2	1	Skeletal muscle necrosis, necrosis, of hippocampus, atrophy of thymus	6	6	1000	NTP, 1988
Mouse/ B6C3F1	571	2719.6	1	Mean body weight lower than those of controls	3	3	5000	NTP, 1988
Mouse/ SPF CD-1	750	4086.0	1	Decreased mean litter and pup weights	8	8	1000	Hazeldon, 1983

*Human equivalent dose (mg/kg/day) from Table 9-1 multiplied by 70 kg to express MED in mg/day for a 70 kg human

TABLE 9-3

Benzyl Alcohol
(CAS No. 100-51-6)

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral, gavage
Species/sex:	rat/male
Dose*:	3605 mg/day
Duration:	103 weeks
Effect:	Increased hyperplasia of the epithelium of the forestomach compared with controls
RV_d:	1
RV_e:	6
CS:	6
RQ:	1000
Reference:	NTP, 1988

*Equivalent human dose

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Wilson, C.L., J.D. Franklin and B.E. Otto. 1987. Fruit volatiles inhibitory to Monilinia fructicola and Botrytis cineren. Plant Dis. 71(4): 316-319.

Wood, E.M. 1954. The toxicity of 3400 chemicals to fish. Fish Toxicity Report No. 1. U.S. Fish and Wildlife Service, Department of the Interior, Leetown, WV. (Cited in Lipnick et. al., 1985)

Yoo, Y.S. 1986. Mutagenic and antimutagenic activities of flavoring agents in foodstuffs. J. Osaka City Med. Center. 34: 267-88.

York, R.G., P.L. Barnwell, M. Pierrera, R.L. Schuler and B.D. Hardin. 1988. Evaluation of twelve chemicals in a preliminary developmental toxicity test. 37: 503-504.

APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB
SCISEARCH
Federal Research in Progress

These searches were conducted in April, 1989, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyons, France.

Jaber, H.M., W.R. Mabey, A.T. Lieu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1987. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1986. Report on Status Report in the Special Review Program, Registration Standards Program and the Data Call in Programs. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

USITC (U.S. International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publ. 1892, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B

Summary Table for Benzyl Alcohol

	Species	Exposure (mg/kg/day)	Effect	RfD or q_1*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ID	ID
Chronic	ID	ID	ID	ID	ID
Carcinogenicity	ID	ID	ID	ID	ID
Oral Exposure					
Subchronic	rat	142.86 for 13 weeks	decrease in body weight compared to control	1.0 mg/kg/day	NTP, 1988
Chronic	rat	142.86 for 103 weeks	hyperplasia of the epithelium of the forestomach	0.3 mg/kg/day	NTP, 1988
Carcinogenicity	rat	285.71	negative	NA	NTP, 1988
REPORTABLE QUANTITIES					
Based on chronic toxicity:		1000			
Based on carcinogenicity:		NA			

ID = Insufficient data; NA = not applicable

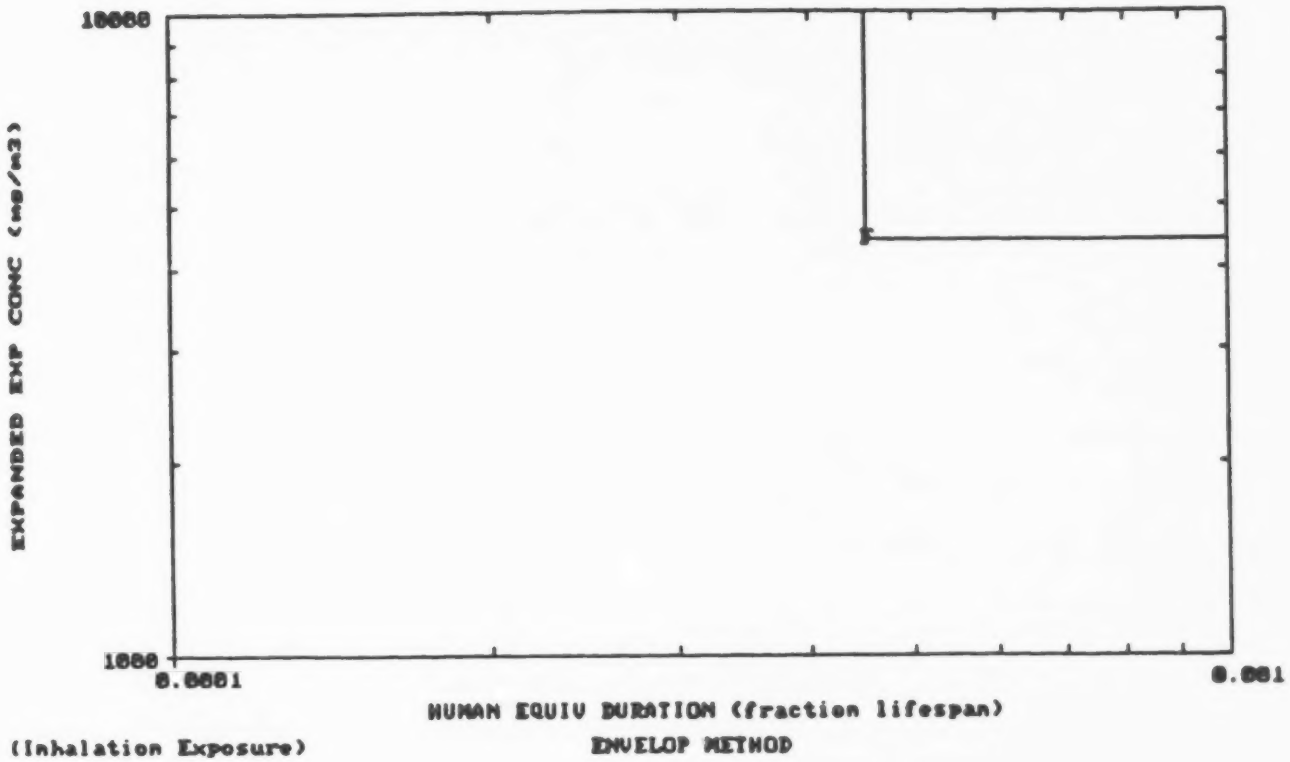
APPENDIX C

DOSE/DURATION RESPONSE GRAPHS FOR EXPOSURE TO BENZYL ALCOHOL

C.1. DISCUSSION

Dose/duration-response graphs for inhalation and oral exposure to benzyl alcohol generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) are presented in Figures C-1 through C-4. Data used to generate these graphs are presented in Section C.2. In the generation of these figures, all responses are classified as adverse (FEL, AEL or LOAEL) or nonadverse (NOEL or NOAEL) for plotting. For inhalation exposure the ordinate expresses concentration in either of two ways. In Figure C-1, the experimental concentration expressed as mg/m^3 was multiplied by the time parameters of the exposure protocol (e.g., hours/day and days/week) and is presented as expanded experimental concentration [expanded exp conc (mg/m^3)]. In Figure C-2, the expanded experimental concentration was multiplied by the cube root of the ratio of the animal: human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975) to estimate an equivalent human or scaled concentration [scaled conc (mg/m^3)]. For oral exposure, the ordinate expresses dosage as human equivalent dose. The animal dosage in mg/kg/day is multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975). The result is then multiplied by 70 kg, the reference human body weight, to express the human equivalent dose as mg/day for a 70 kg human.

The boundary for adverse effects (solid line) is drawn by identifying the lowest adverse effect dose or concentration at the shortest duration of exposure at which an adverse effect occurred. From this point, an infinite

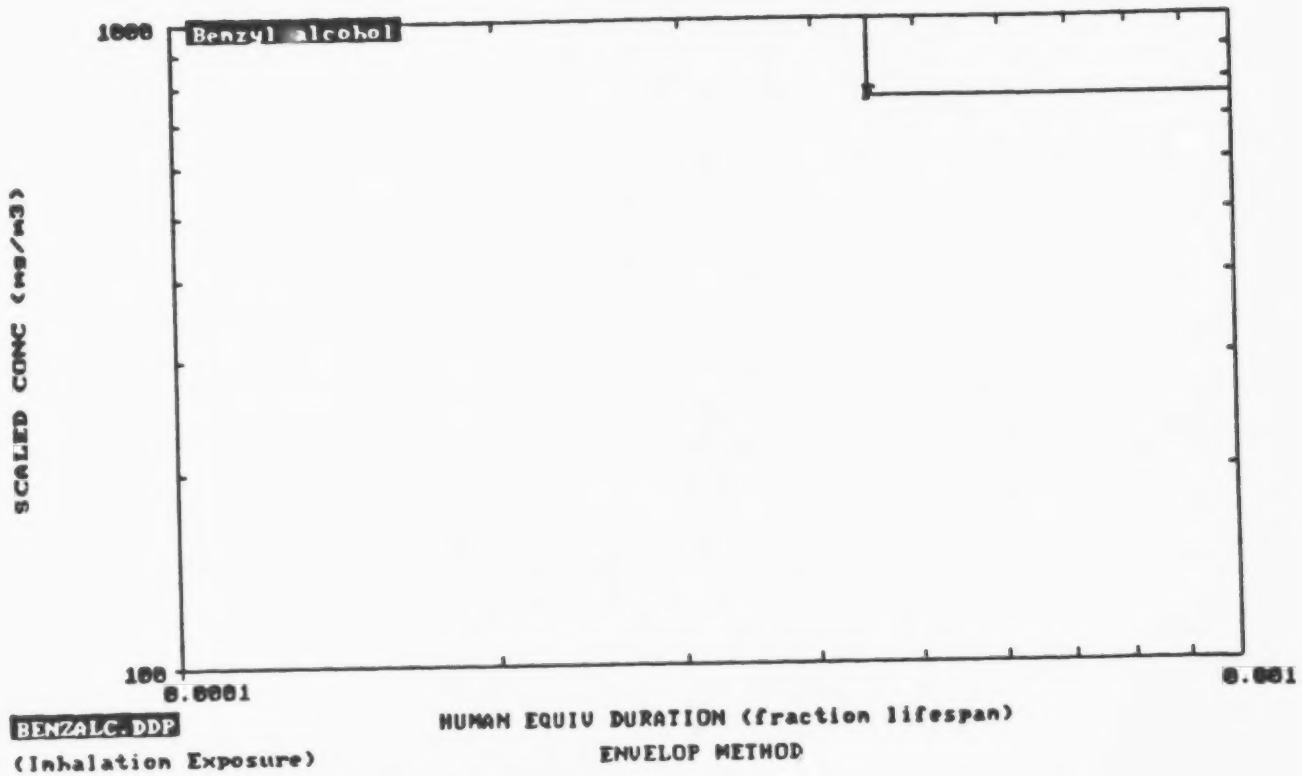


Key: F = FEL

Solid Line = Adverse Effects Boundary

FIGURE C-1

Dose/Duration Response Graph for Inhalation Exposure to
Benzyl Alcohol, Expanded Concentration

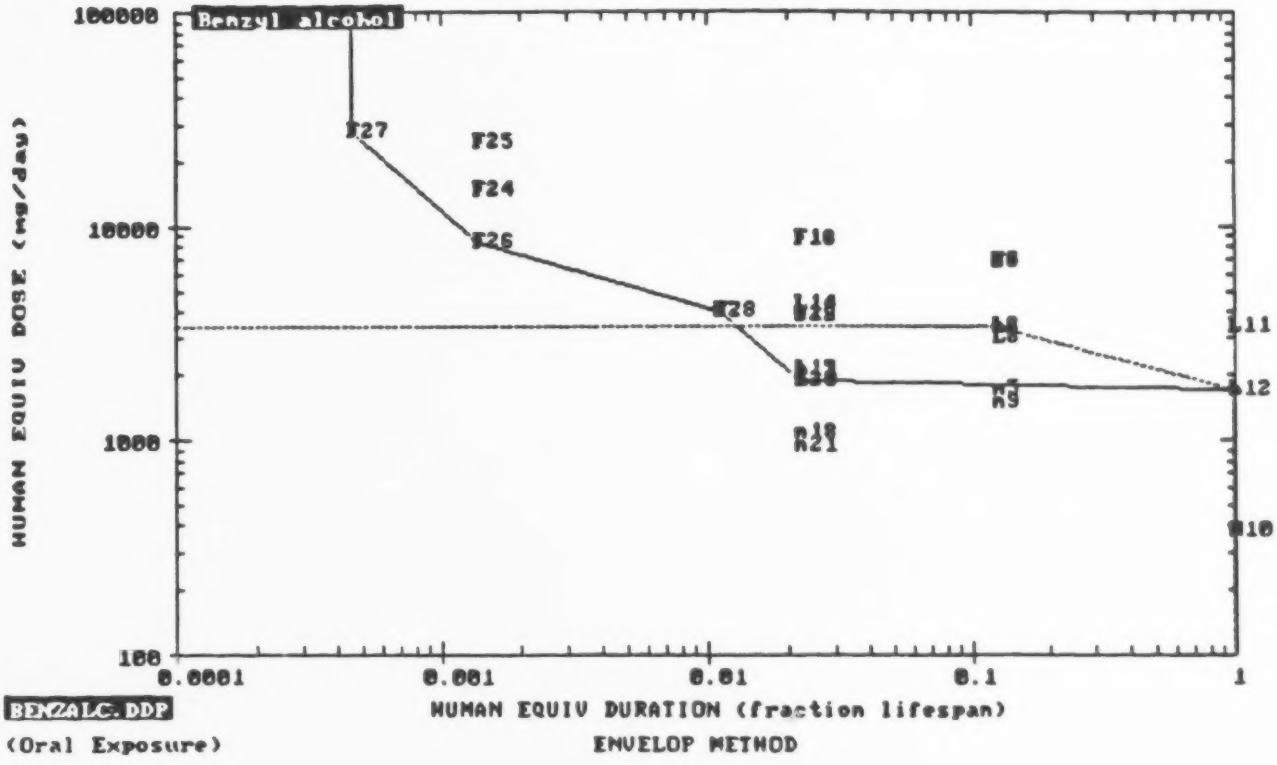


Key: F = FEL

Solid Line = Adverse Effects Boundary

FIGURE C-2

Dose/Duration Response Graph for Inhalation Exposure to
Benzyl Alcohol, Scaled Concentration

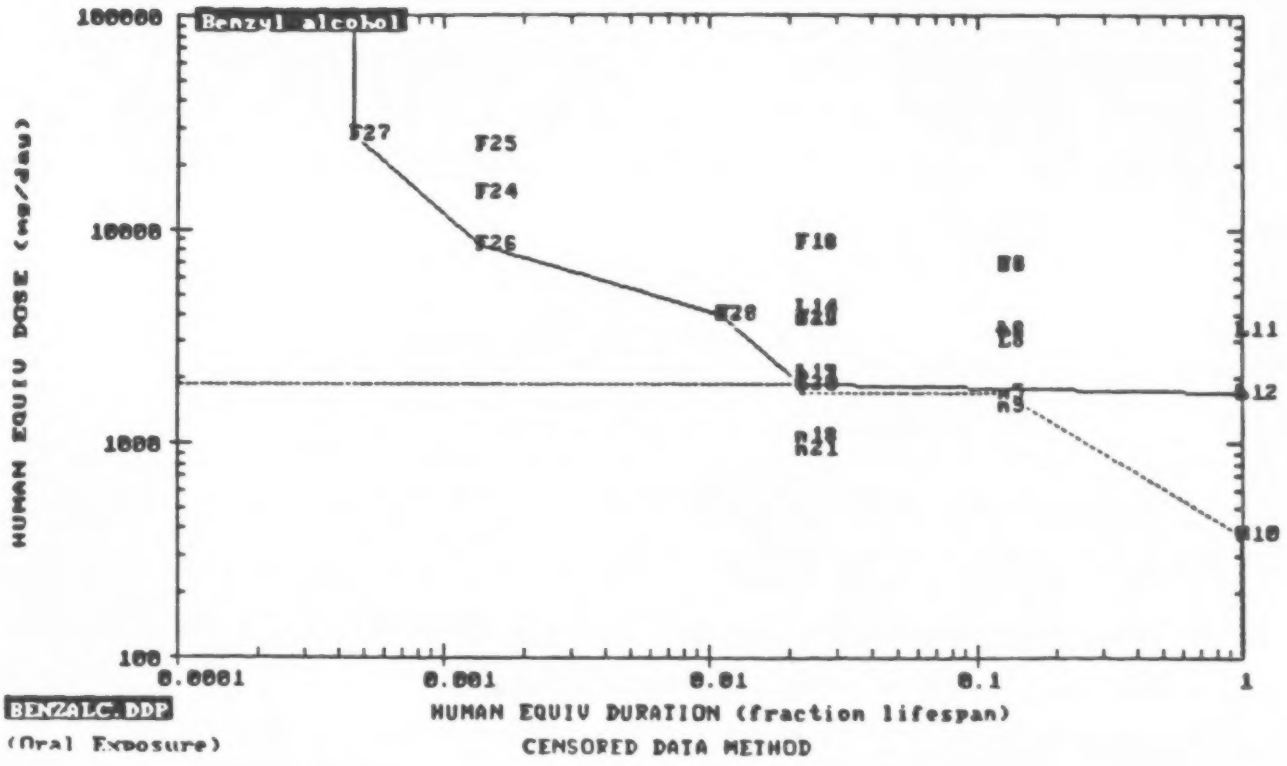


Key: N = NOEL
L = LOEL
F = FEL

Solid Line = Adverse Effects Boundary
Dashed Line = No Adverse Effects Boundary

FIGURE C-3

Dose/Duration Response Graph for Oral Exposure to
Benzyl Alcohol, Envelope Method



Key: N = NOEL
L = LOEL
F = FEL

Solid Line = Adverse Effects Boundary
Dashed Line = No Adverse Effects Boundary

FIGURE C-4

Dose/Duration Response Graph for Oral Exposure to
Benzyl Alcohol, Censored Date Method

line is extended upward, parallel to the dose axis. The starting point is then connected to the lowest adverse effect dose or concentration at the next longer duration of exposure that has an adverse effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest adverse effect dose or concentration. From this point, a line is extended to the right, parallel to the duration axis. The region of adverse effects lies above the adverse effects boundary.

Using the envelope method, the boundary for no adverse effects (dashed line) is drawn by identifying the highest no adverse effects dose or concentration. From this point, a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next lower or equal no adverse effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line is dropped parallel to the dose or concentration axis to the duration axis. The no adverse effects region lies below the no adverse effects boundary. At either ends of the graph between the adverse effects and no adverse effects boundaries are regions of ambiguity. The area (if any) resulting from intersection of the adverse effects and no adverse effects boundaries is defined as the region of contradiction.

In the censored data method, all no adverse effect points located in the region of contradiction are dropped from consideration and the no adverse effect boundary is redrawn so that it does not intersect the adverse effects boundary and no region of contradiction is generated. This method results in the most conservative definition of the no adverse effects region.

As seen from Figures C-1 and C-2, only one data point was available for inhalation exposure. Figure C-3 presents the dose-duration response graph generated by the envelope method. The adverse effects boundary is defined

by five points, corresponding to an LD_{50} in rabbits of 1040 mg/kg (Graham and Kuizenga, 1945) (Rec. #27), a mouse LD_{50} of 1580 mg/kg (Jenner et al., 1964) (Rec. #26), maternal mortality and body weight decrease in mice gavaged with 750 mg/kg during days 7-14 of gestation, decreased litter and pup weights (Hazelden, 1983) (Rec. #7), rough hair coat in female rats given 250 mg/kg 5 days/week for 16 days (NTP, 1988) (Rec. #17) and increased mortality in female rats gavaged with 200 mg/kg 5 days/week for 103 weeks (NTP, 1988) (Rec. #1). The no effects boundary is defined by two points one representing no effects observed in male rats at dose levels $\leq$400 mg/kg given 5 days a week for 91 days (NTP, 1988) (Rec. #6), and the other representing the 2-year study by NTP (1988) where no effects were seen in male mice at the 100 mg/kg dosage given 5 days a week (Rec. #10). The region of contradiction contains some LOAELs, NOAELs and NOELs.

When the graph is redrawn to eliminate the region of contradiction (see Figure C-4), the no adverse effects boundary is defined by the points representing the dose levels of 200 mg/kg 5 days/week for 91 days (Rec. #2) and 200 mg/kg, 5 days/week for 2 years (Rec. #12), both given to male rats for 2 years and producing no observed effects (NTP, 1988).

C.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

C.2.1. Inhalation Exposure.

Chemical Name: Benzyl Alcohol
CAS Number: 100-51-6
Document Title: Health and Environmental Effects Document for Benzyl Alcohol
Document Number: Pending
Document Date: Pending
Document Type: HEED

==========

RECORD #1:

Species:	Rats	Dose:	4422.000
Sex:	NR	Duration Exposure:	0.3 days
Effect:	FEL	Duration Observation:	14.0 days
Route:	Inhalation		

Number Exposed:	6
Number Responses:	3
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Acute inhalation toxicity reported; no other endpoints. Maximum inhalation of saturated vapor 2 hours without death.

Citation: Smyth et al., 1951

C.2.2. Oral Exposure.

Chemical Name: Benzyl alcohol
CAS Number: 100-51-6
Document Title: Health and Environmental Effects Document for Benzyl Alcohol
Document Number: Pending
Document Date: Pending
Document Type: HEED

==========

RECORD #1:

Species:	Rats	Dose:	143.000
Sex:	Female	Duration Exposure:	103.0 weeks
Effect:	LOAEL	Duration Observation:	103.0 weeks
Route:	Gavage		

Number Exposed:	50
Number Responses:	33
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Doses given: 0, 200, 400 mg/kg/day x 5 days/week = 0, 143, 286 mg/kg/day. Nonaccidental deaths: control, 13; low, 16; high, 20/50. Accidental deaths 1, 17, 13/50. LOAEL basis for chronic RfD.

Citation: NTP, 1988

RECORD #2:

Species:	Rats	Dose:	143.000
Sex:	Female	Duration Exposure:	91.0 days
Effect:	NOAEL	Duration Observation:	91.0 days
Route:	Gavage		

Number Exposed:	0
Number Responses:	9
Type of Effect:	WGTDC
Site of Effect:	BODY
Severity Effect:	4

Comment: Dosages: 0, 50, 100, 200, 400, 800 mg/kg 5 days/week = 0, 36, 71, 143, 286, 571 mg/kg/day. NOAEL is basis for subchronic RfD.

Citation: NTP, 1988

RECORD #3:

Species:	Rats	Dose:	571.000
Sex:	Male	Duration Exposure:	91.0 days
Effect:	FEL	Duration Observation:	91.0 days
Route:	Gavage		

Number Exposed:	10	10	9	10	9
Number Responses:	4	5	9	8	6
Type of Effect:	DEATH	NECRO	NECRO	ATROP	FUNP
Site of Effect:	BODY	MSKEL	BRAIN	THYMS	KIDNY
Severity Effect:	10	8	8	8	8

Comment: Four additional deaths attributed to gavage procedure. None of the histopathologic effects occurred at lower doses.

Citation: NTP, 1988

RECORD #4:

Species:	Rats	Dose:	571.000
Sex:	Female	Duration Exposure:	91.0 days
Effect:	AEL	Duration Observation:	91.0 days
Route:	Gavage		

Number Exposed:	7
Number Responses:	7
Type of Effect:	NECRO
Site of Effect:	BRAIN
Severity Effect:	8

Comment: Other effects: final mean body weights 5% lower than controls; staggering and lethargy following dosing. See Rec. #2 for dosing schedule.

Citation: NTP, 1988

RECORD #5:

Species:	Rats	Dose:	286.000
Sex:	Female	Duration Exposure:	91.0 days
Effect:	LOAEL	Duration Observation:	91.0 days

Number Exposed:	9
Number Responses:	9
Type of Effect:	WGTDC
Site of Effect:	BODY
Severity Effect:	4

Comment: See Rec. #2.

Citation: NTP, 1988

RECORD #6:

Species:	Rats	Dose:	286.000
Sex:	Male	Duration Exposure:	91.0 days
Effect:	NOAEL	Duration Observation:	91.0 days
Route:	Gavage		

Number Exposed:	10	9	10	9	10
Number Responses:	0	0	0	0	0
Type of Effect:	DEATH	NECRO	ATROP	FUNP	NECRO
Site of Effect:	BODY	BRAIN	THYMS	KIDNY	MSKEL
Severity Effect:	10	8	8	8	8

Comment: No histopathologic effects at doses <571 mg/kg/day. One male died in 200 mg/kg dose group (143 mg/kg/day) after dosing.

Citation: NTP, 1988

RECORD #7:

Species:	Mice	Dose:	750.000
Sex:	Female	Duration Exposure:	8.0 days
Effect:	AEL	Duration Observation:	21.0 days
Route:	Gavage		

Number Exposed:	19	21	21
Number Responses:	50	21	21
Type of Effect:	DEATH	WGTDC	REPRO
Site of Effect:	BODY	BODY	FETUS
Severity Effect:	10	4	9

Comment: Maternal toxicity on treatment days 7-14: hunched, tremors, subdued, prostrate, dyspnoea, swollen and cyanotic abdomen, piloerection, cyanosis. Increased maternal toxicity: 19/50 vs. 0/50 controls.

Citation: Hazelden, 1983

RECORD #8:

Species:	Mice	Dose:	571.000
Sex:	Female	Duration Exposure:	91.0 days
Effect:	LOAEL	Duration Observation:	91.0 days
Route:	Gavage		

Number Exposed:	8
Number Responses:	8
Type of Effect:	WGTDC
Site of Effect:	BODY
Severity Effect:	4

Comment: Dosages: 0, 50, 100, 200, 400, 800 mg/kg x 5 days/week = 0, 36, 71, 143, 286, 571 mg/kg/day. Final mean body weight 8% lower than controls. Signs of neurotoxicity after dosing.

Citation: NTP, 1988

RECORD #9:

Species:	Mice	Dose:	286.000
Sex:	Female	Duration Exposure:	91.0 days
Effect:	NOAEL	Duration Observation:	91.0 days
Route:	Gavage		

Number Exposed:	9
Number Responses:	0
Type of Effect:	WGTDC
Site of Effect:	BODY
Severity Effect:	4

Comment: Final mean body weight 5% lower than controls. No compound-related histopathological effects were observed.

Citation: NTP, 1988

RECORD #10:

Species:	Mice	Dose:	71.000
Sex:	Female	Duration Exposure:	103.0 weeks
Effect:	NOEL	Duration Observation:	103.0 weeks
Route:	Gavage		

Number Exposed:	50
Number Responses:	0
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Doses were 100 and 200 mg/kg, 5 days/week.

Citation: NTP, 1988

RECORD #11:

Species:	Rats	Dose:	286.000
Sex:	Male	Duration Exposure:	103.0 weeks
Effect:	LOAEL	Duration Observation:	103.0 weeks
Route:	Gavage		

Number Exposed:	50
Number Responses:	4
Type of Effect:	HYPRP
Site of Effect:	COLON
Severity Effect:	3

Comment: Hyperplasia of the epithelium of the forestomach. Doses were 200 and 400 mg/kg, 5 days/week.

Citation: NTP, 1988

RECORD #12:

Species:	Rats	Dose:	143.000
Sex:	Male	Duration Exposure:	103.0 weeks
Effect:	NOAEL	Duration Observation:	103.0 weeks
Route:	Gavage		

Number Exposed:	50
Number Responses:	0
Type of Effect:	HYPRP
Site of Effect:	COLON
Severity Effect:	3

Comment: See Rec. #11.

Citation: NTP, 1988

RECORD #13:

Species:	Rats	Dose:			714.000
Sex:	Male	Duration Exposure:			16.0 days
Effect:	FEL	Duration Observation:			16.0 days
Route:	Gavage				

Number Exposed:	5	5	5	5	5
Number Responses:	2	NR	NR	NR	NR
Type of Effect:	DEATH	BEHAV	WGTDC	HEMOR	IRRIT
Site of Effect:	BODY	BODY	BODY	CARDV	COLON
Severity Effect:	10	7	4	5	5

Comment: Doses were 125, 250, 500, 1000, 2000 mg/kg, 5 days/week. Effects were seen at $\geq$1000 mg/kg.

Citation: NTP, 1988

RECORD #14:

Species:	Rats	Dose:	357.000
Sex:	Male	Duration Exposure:	16.0 days
Effect:	LOAEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5
Number Responses:	NR
Type of Effect:	FUNS
Site of Effect:	SKIN
Severity Effect:	2

Comment: Rough hair coat the only effect observed at 500 mg/kg.

Citation: NTP, 1988

RECORD #15:

Species:	Rats	Dose:	179.000
Sex:	Male	Duration Exposure:	16.0 days
Effect:	NOAEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5
Number Responses:	0
Type of Effect:	FUNS
Site of Effect:	SKIN
Severity Effect:	2

Comment: See Rec. #13.

Citation: NTP, 1988

RECORD #16:

Species:	Rats	Dose:	714.000
Sex:	Female	Duration Exposure:	16.0 days
Effect:	FEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5
Number Responses:	3
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: See Rec. #13.

Citation: NTP, 1988

RECORD #17:

Species:	Rats	Dose:	179.000
Sex:	Female	Duration Exposure:	16.0 days
Effect:	LOAEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5
Number Responses:	NR
Type of Effect:	FUNS
Site of Effect:	SKIN
Severity Effect:	2

Comment: Rough hair coat was the only effect noted. See Rec. #13.

Citation: NTP, 1988

RECORD #18:

Species:	Rats	Dose:	89.000
Sex:	Female	Duration Exposure:	16.0 days
Effect:	NOAEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5
Number Responses:	0
Type of Effect:	FUNS
Site of Effect:	SKIN
Severity Effect:	2

Comment: See Rec. #13.

Citation: NTP, 1988

RECORD #19:

Species:	Mice	Dose:	714.000
Sex:	Male	Duration Exposure:	16.0 days
Effect:	AEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5
Number Responses:	1
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: All mice at the next higher dose level (1429 mg/kg) died. None of the control mice died.

Citation: NTP, 1988

RECORD #20:

Species:	Mice	Dose:	357.000
Sex:	Male	Duration Exposure:	16.0 days
Effect:	LOAEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5	5
Number Responses:	NR	NR
Type of Effect:	BEHAV	FUNS
Site of Effect:	BODY	SKIN
Severity Effect:	7	2

Comment: Dosages: 0, 125, 250, 500, 1000, 2000 mg/kg x 5 days/week = 0, 89, 179, 357, 714, 1429 mg/kg/day. No compound-related histopathological effects seen.

Citation: NTP, 1988

RECORD #21:

Species:	Mice	Dose:	178.000
Sex:	Male	Duration Exposure:	16.0 days
Effect:	NOAEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5	5
Number Responses:	0	0
Type of Effect:	BEHAV	FUNS
Site of Effect:	BODY	SKIN
Severity Effect:	7	2

Comment: See Rec. #20.

Citation: NTP, 1988

RECORD #22:

Species:	Mice	Dose:	714.000
Sex:	Female	Duration Exposure:	16.0 days
Effect:	FEL	Duration Observation:	16.0 days
Route:	Gavage		

Number Exposed:	5	5	5	5
Number Responses:	2	NR	NR	NR
Type of Effect:	DEATH	BEHAV	IRRIT	FUNS
Site of Effect:	BODY	BODY	OTHER	SKIN
Severity Effect:	10	7	5	2

Comment: All animals died in 2000 mg/kg groups of both sexes. Lethargy and rough hair coats were seen; also blood in the urinary bladder. See Rec. #20.

Citation: NTP, 1988

RECORD #23:

Species:	Mice		Dose:		357.000
Sex:	Female		Duration Exposure:		16.0 days
Effect:	NOAEL		Duration Observation:		16.0 days
Route:	Gavage				
Number Exposed:	5	5	5	5	
Number Responses:	0	0	0	0	
Type of Effect:	DEATH	BEHAV	IRRIT	FUNS	
Site of Effect:	BODY	BODY	OTHER	SKIN	
Severity Effect:	10	7	5	2	

Comment: See Rec. #20.

Citation: NTP, 1988

RECORD #24:

Species:	Rats	Dose:		1230.000
Sex:	Both	Duration Exposure:		1.0 days
Effect:	FEL	Duration Observation:		14.0 days
Route:	Gavage			
Number Exposed:	10			
Number Responses:	NR			
Type of Effect:	DEATH			
Site of Effect:	BODY			
Severity Effect:	10			

Comment: Depression and then coma within 10-15 minutes. Excitable for 3-4 days.

Citation: Jenner et al., 1964

RECORD #25:

Species:	Rats	Dose:		2080.000
Sex:	NR	Duration Exposure:		1.0 days
Effect:	FEL	Duration Observation:		1.0 days
Route:	Gavage			
Number Exposed:	20			
Number Responses:	NR			
Type of Effect:	DEATH			
Site of Effect:	BODY			
Severity Effect:	10			

Comment:

Citation: Graham and Kuizenga, 1945

RECORD #26:

Species:	Mice	Dose:	1580.000
Sex:	NR	Duration Exposure:	1.0 day
Effect:	FEL	Duration Observation:	14.0 days
Route:	Gavage		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Depression; death occurred within 2-18 hours.

Citation: Jenner et al., 1964

RECORD #27:

Species:	Rabbits	Dose:	1040.000
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Gavage		

Number Exposed:	9
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment:

Citation: Graham and Kuizenga, 1945

NR = Not reported